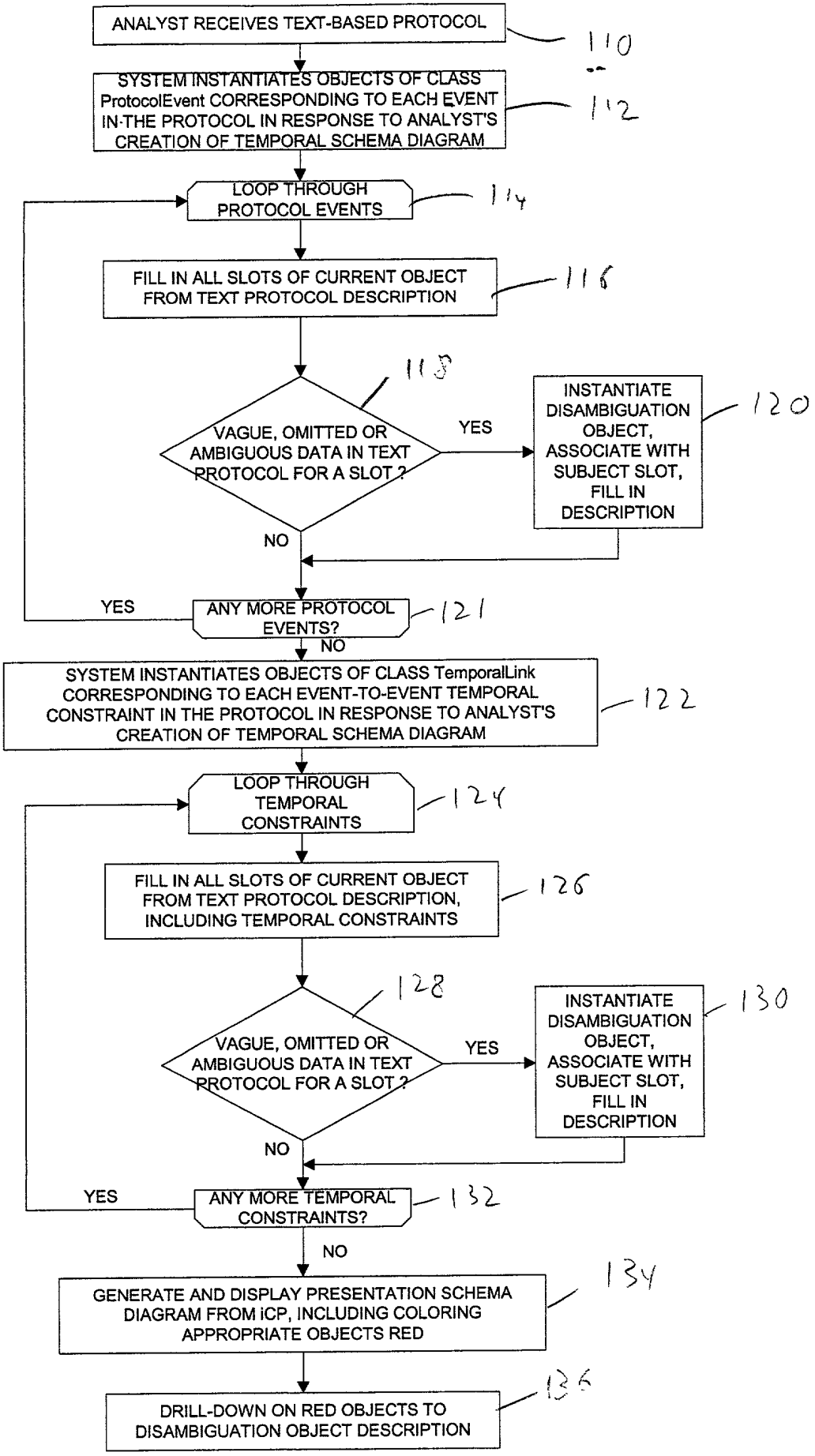

ANALYST RECEIVES TEXT-BASED PROTOCOL
110
SYSTEM INSTANTIATES OBJECTS OF CLASS ProtocolEvent CORRESPONDING TO EACH EVENT IN THE PROTOCOL IN RESPONSE TO ANALYST'S CREATION OF TEMPORAL SCHEMA DIAGRAM
112
LOOP THROUGH PROTOCOL EVENTS
114
FILL IN ALL SLOTS OF CURRENT OBJECT FROM TEXT PROTOCOL DESCRIPTION
116
VAGUE, OMITTED OR AMBIGUOUS DATA IN TEXT PROTOCOL FOR A SLOT ?
118
YES
INSTANTIATE DISAMBIGUATION OBJECT, ASSOCIATE WITH SUBJECT SLOT, FILL IN DESCRIPTION
120
NO
YES
ANY MORE PROTOCOL EVENTS?
121
NO
SYSTEM INSTANTIATES OBJECTS OF CLASS TemporalLink CORRESPONDING TO EACH EVENT-TO-EVENT TEMPORAL CONSTRAINT IN THE PROTOCOL IN RESPONSE TO ANALYST'S CREATION OF TEMPORAL SCHEMA DIAGRAM
122
LOOP THROUGH TEMPORAL CONSTRAINTS
124
FILL IN ALL SLOTS OF CURRENT OBJECT FROM TEXT PROTOCOL DESCRIPTION, INCLUDING TEMPORAL CONSTRAINTS
126
VAGUE, OMITTED OR AMBIGUOUS DATA IN TEXT PROTOCOL FOR A SLOT ?
128
YES
INSTANTIATE DISAMBIGUATION OBJECT, ASSOCIATE WITH SUBJECT SLOT, FILL IN DESCRIPTION
130
NO
YES
ANY MORE TEMPORAL CONSTRAINTS?
132
NO
GENERATE AND DISPLAY PRESENTATION SCHEMA DIAGRAM FROM iCP, INCLUDING COLORING APPROPRIATE OBJECTS RED
134
DRILL-DOWN ON RED OBJECTS TO DISAMBIGUATION OBJECT DESCRIPTION
136

Fig. 1

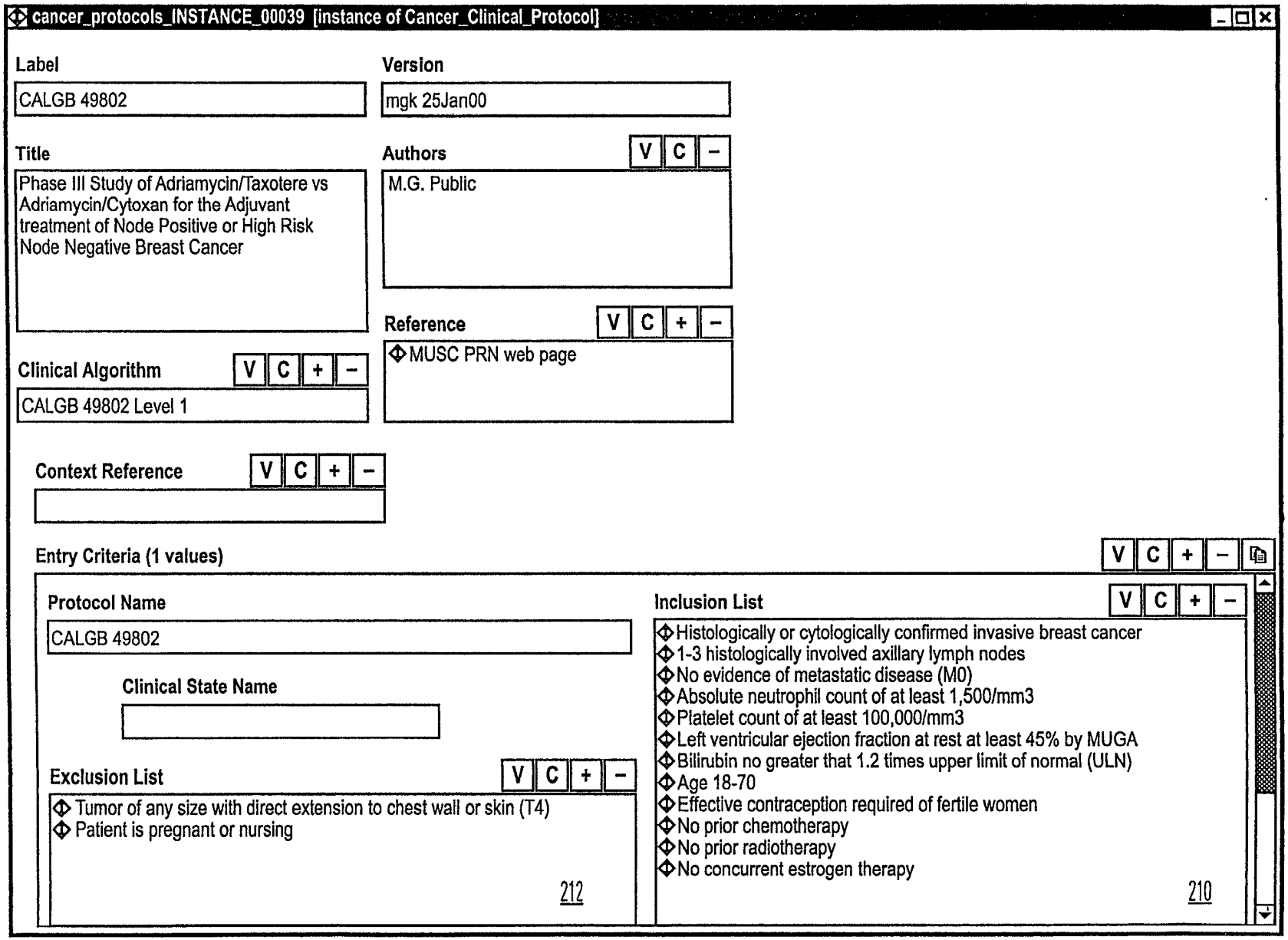


FIG. 2

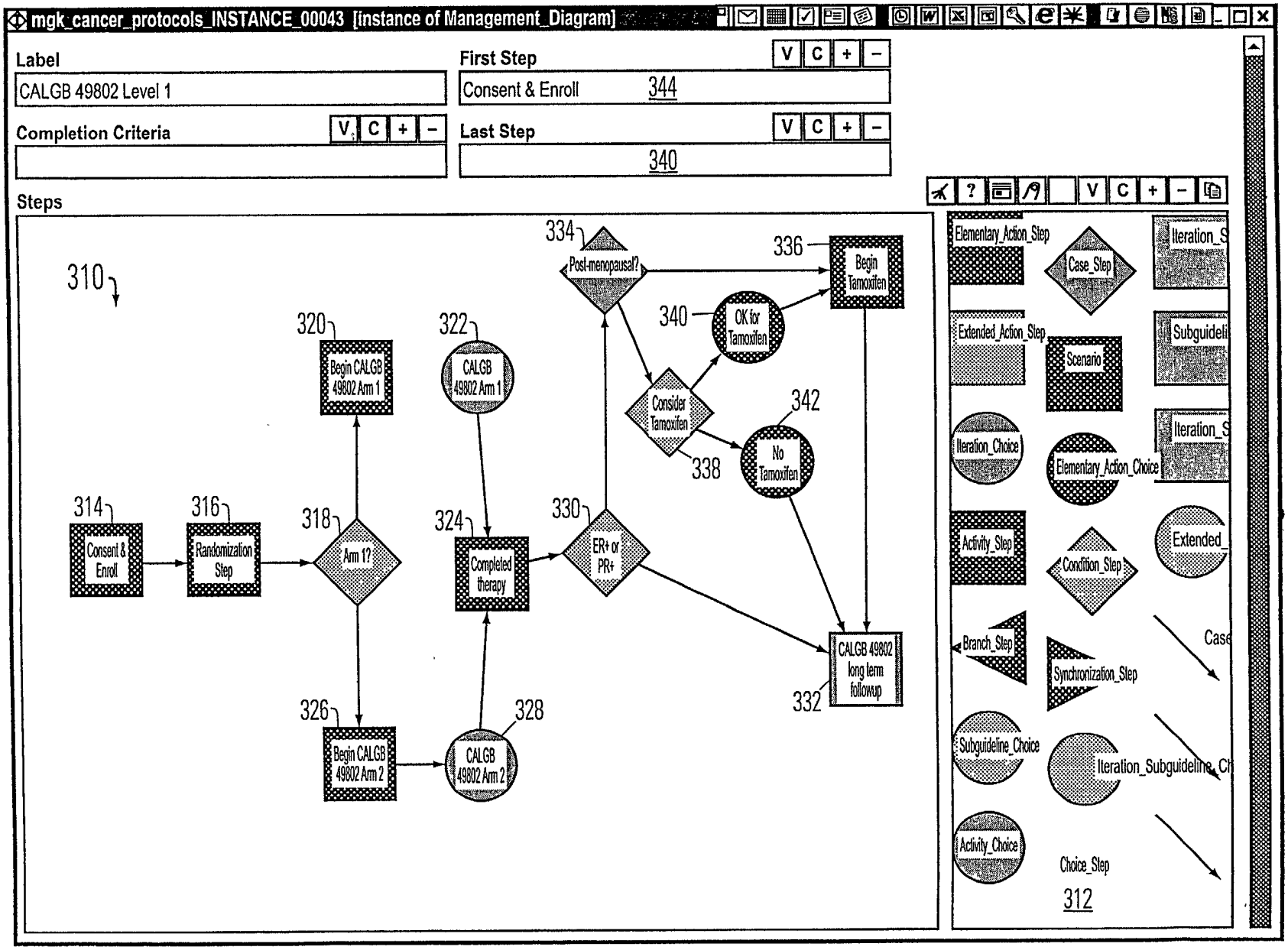


FIG. 3

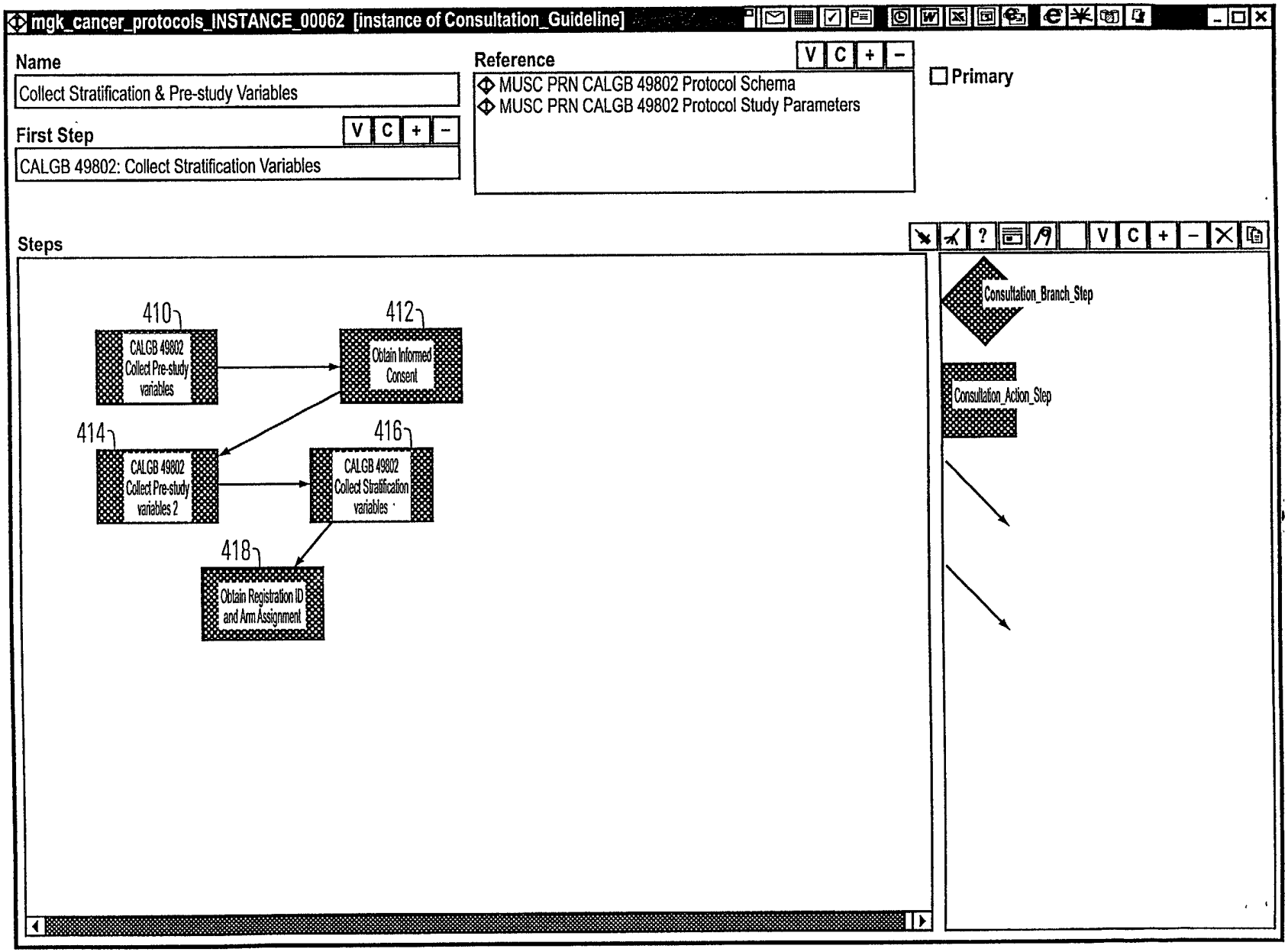


FIG. 4

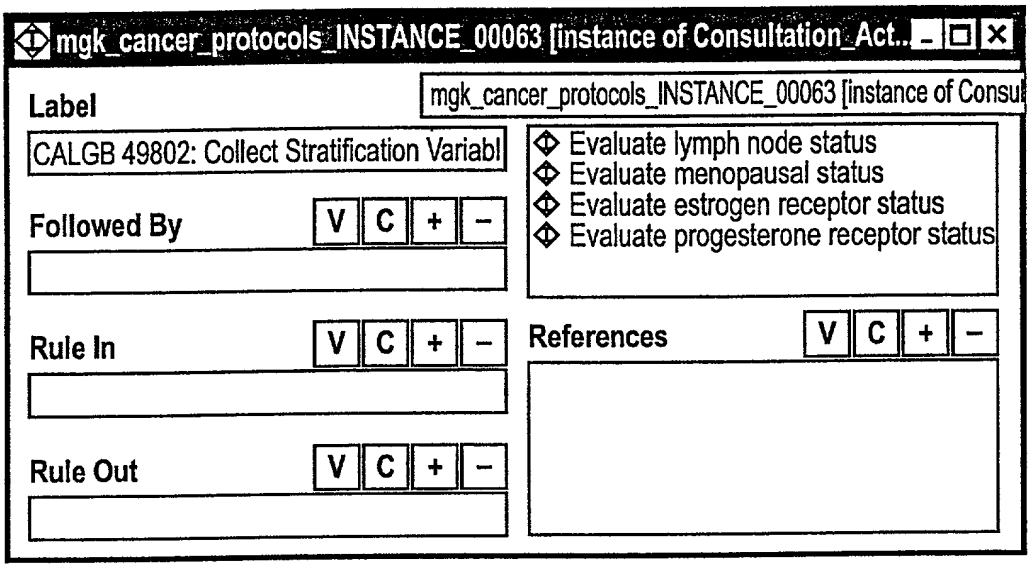

mgk_cancer_protocols_INSTANCE_00063 [instance of Consultation_Act..
Label
mgk_cancer_protocols_INSTANCE_00063 [instance of Consul
CALGB 49802: Collect Stratification Variabl
Evaluate lymph node status
Evaluate menopausal status
Evaluate estrogen receptor status
Evaluate progesterone receptor status
Followed By
V
C
+
–
Rule In
V
C
+
–
References
V
C
+
–
Rule Out
V
C
+
–

FIG. 5

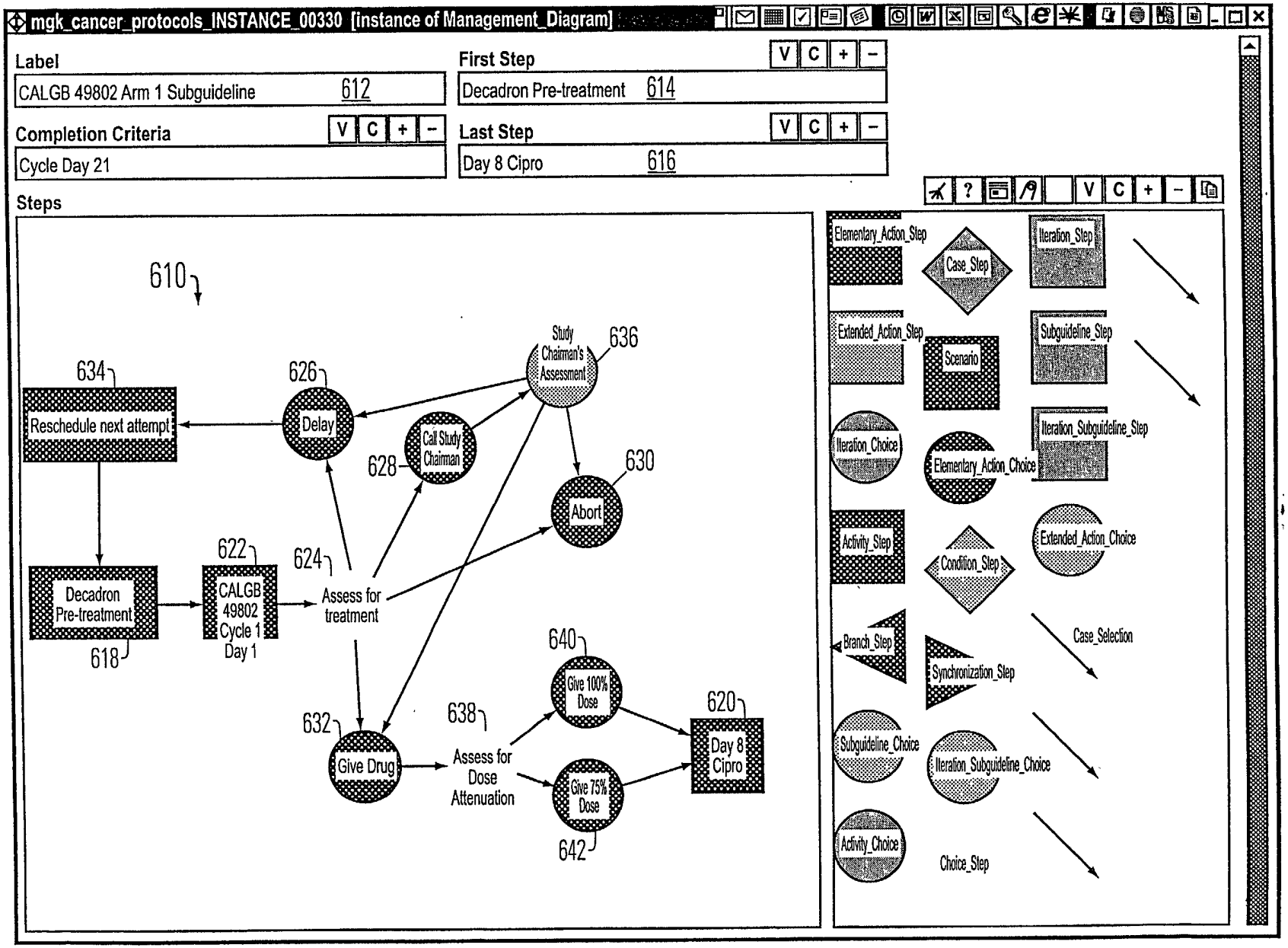

mgk_cancer_protocols_INSTANCE_00330 [instance of Management_Diagram]
Label
CALGB 49802 Arm 1 Subguideline
612
First Step
Decadron Pre-treatment
614
Completion Criteria
Cycle Day 21
Last Step
Day 8 Cipro
616
Steps
610
634
Reschedule next attempt
626
Delay
636
Study Chairman's Assessment
628
Call Study Chairman
630
Abort
618
Decadron Pre-treatment
622
CALGB 49802 Cycle 1 Day 1
624
Assess for treatment
632
Give Drug
638
Assess for Dose Attenuation
640
Give 100% Dose
642
Give 75% Dose
620
Day 8 Cipro
Elementary_Action_Step
Case_Step
Iteration_Step
Extended_Action_Step
Scenario
Subguideline_Step
Iteration_Choice
Elementary_Action_Choice
Iteration_Subguideline_Step
Activity_Step
Condition_Step
Extended_Action_Choice
Branch_Step
Synchronization_Step
Case_Selection
Subguideline_Choice
Iteration_Subguideline_Choice
Activity_Choice
Choice_Step

FIG. 6

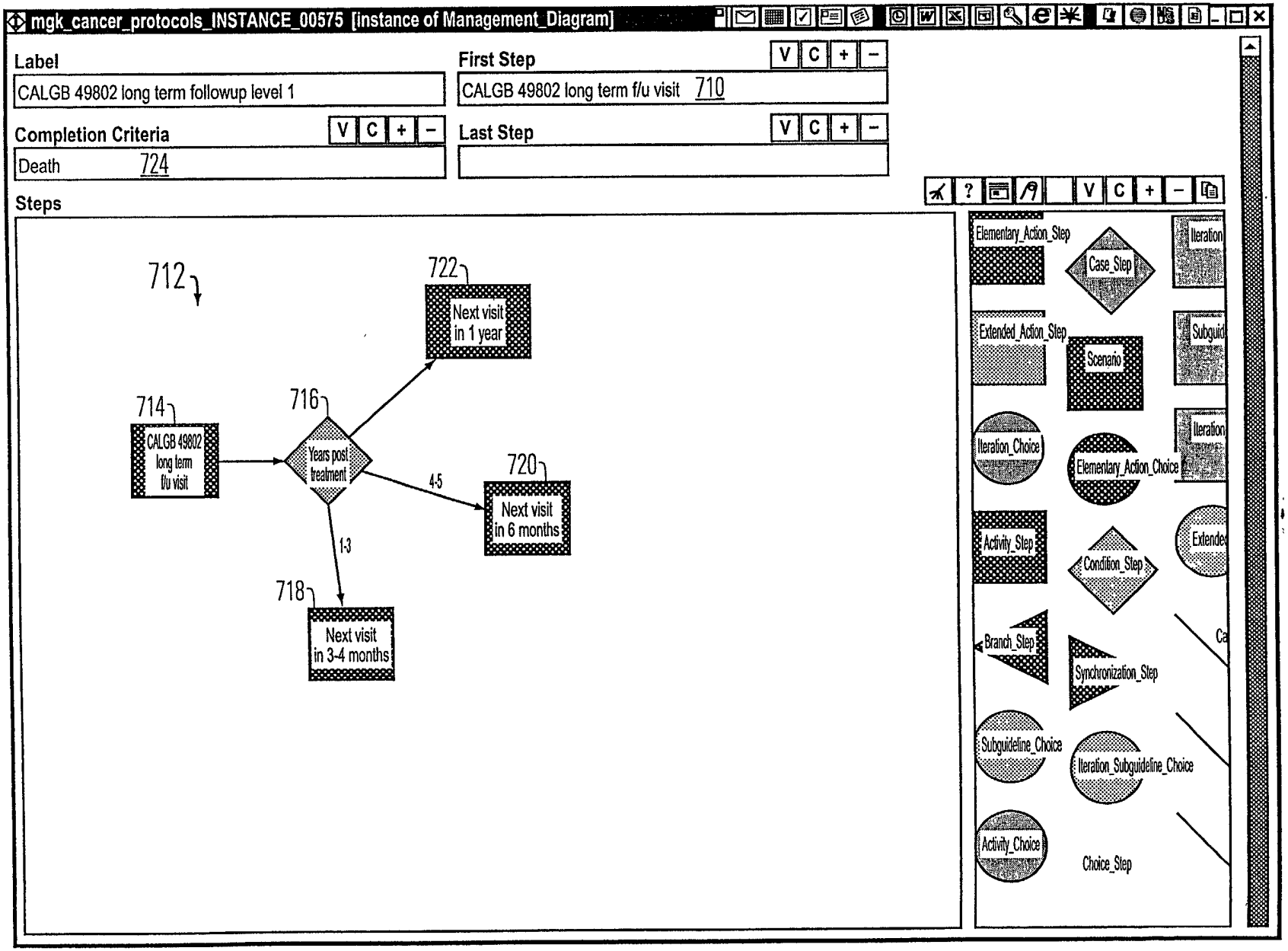


FIG. 7

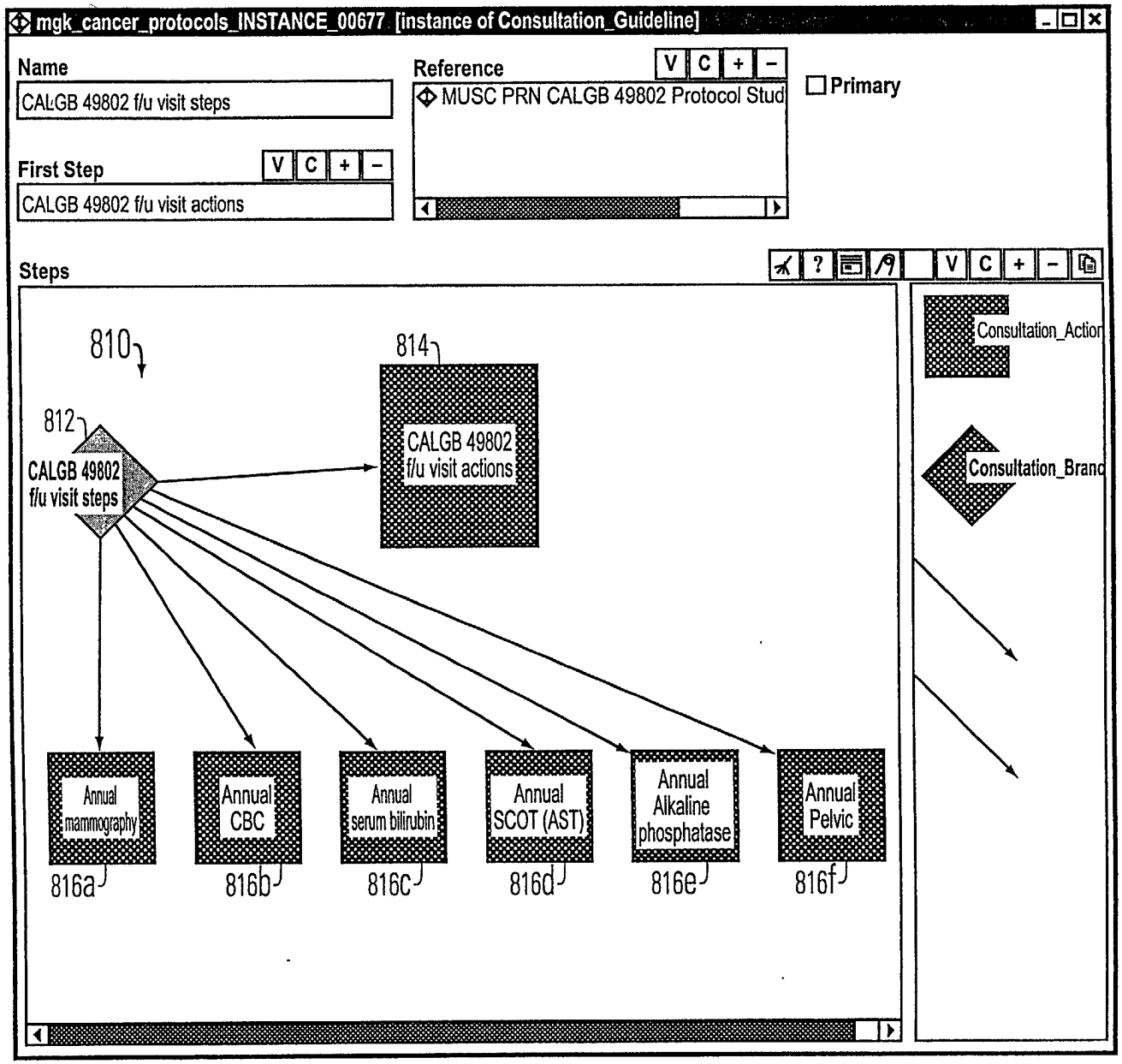


FIG. 8

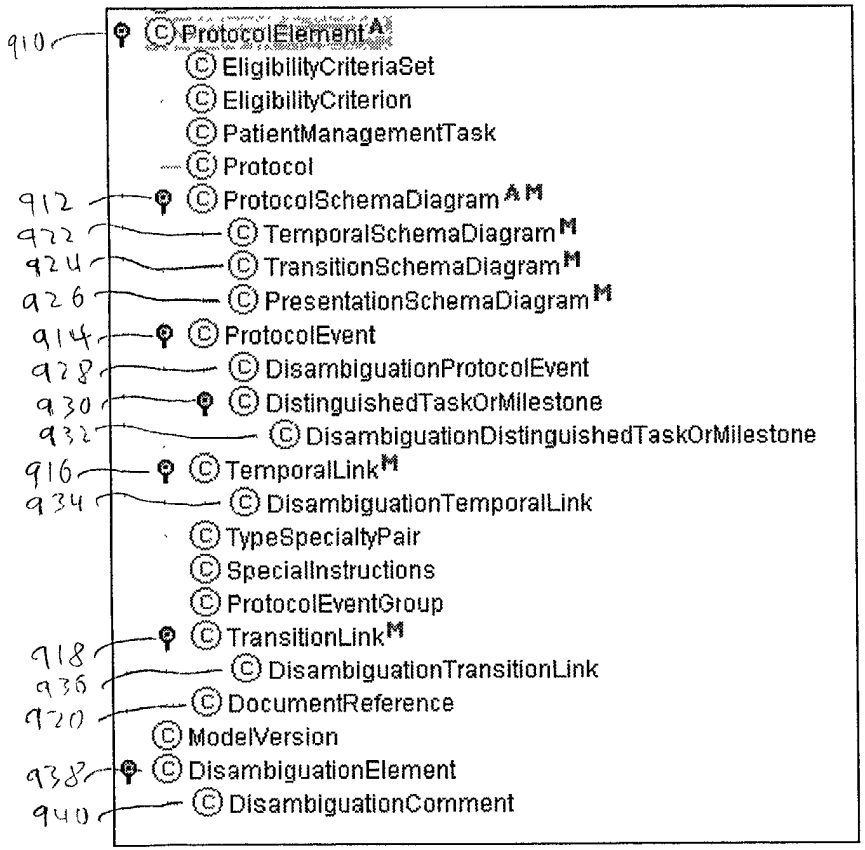

910
ProtocolElement A
EligibilityCriteriaSet
EligibilityCriterion
PatientManagementTask
Protocol
912
ProtocolSchemaDiagram A M
922
TemporalSchemaDiagram M
924
TransitionSchemaDiagram M
926
PresentationSchemaDiagram M
914
ProtocolEvent
928
DisambiguationProtocolEvent
930
DistinguishedTaskOrMilestone
932
DisambiguationDistinguishedTaskOrMilestone
916
TemporalLink M
934
DisambiguationTemporalLink
TypeSpecialtyPair
SpecialInstructions
ProtocolEventGroup
TransitionLink M
918
DisambiguationTransitionLink
936
DocumentReference
920
ModelVersion
938
DisambiguationElement
940
DisambiguationComment

Fig. 9

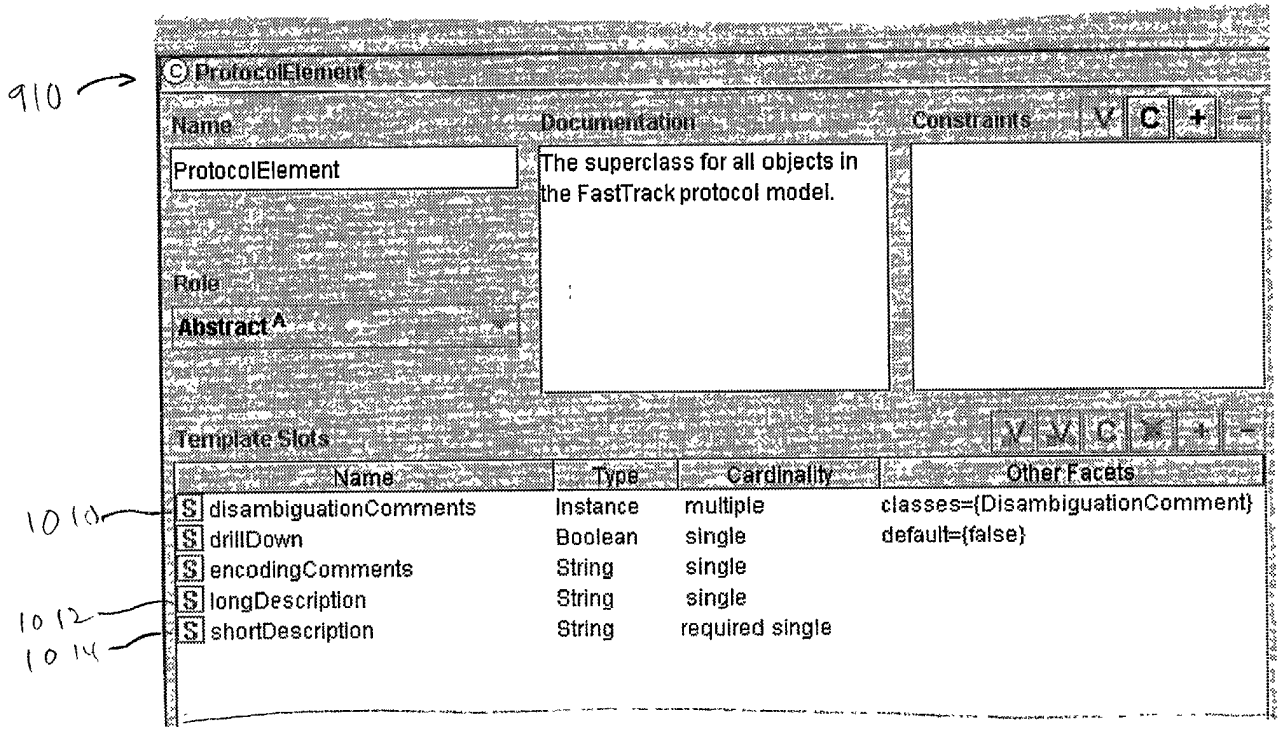

910
ProtocolElement
Name
Documentation
Constraints
ProtocolElement
The superclass for all objects in the FastTrack protocol model.
Role
Abstract
Template Slots
Name
Type
Cardinality
Other Facets
1010
disambiguationComments
Instance
multiple
classes={DisambiguationComment}
drillDown
Boolean
single
default={false}
encodingComments
String
single
1012
longDescription
String
single
1014
shortDescription
String
required single

Fig. 10

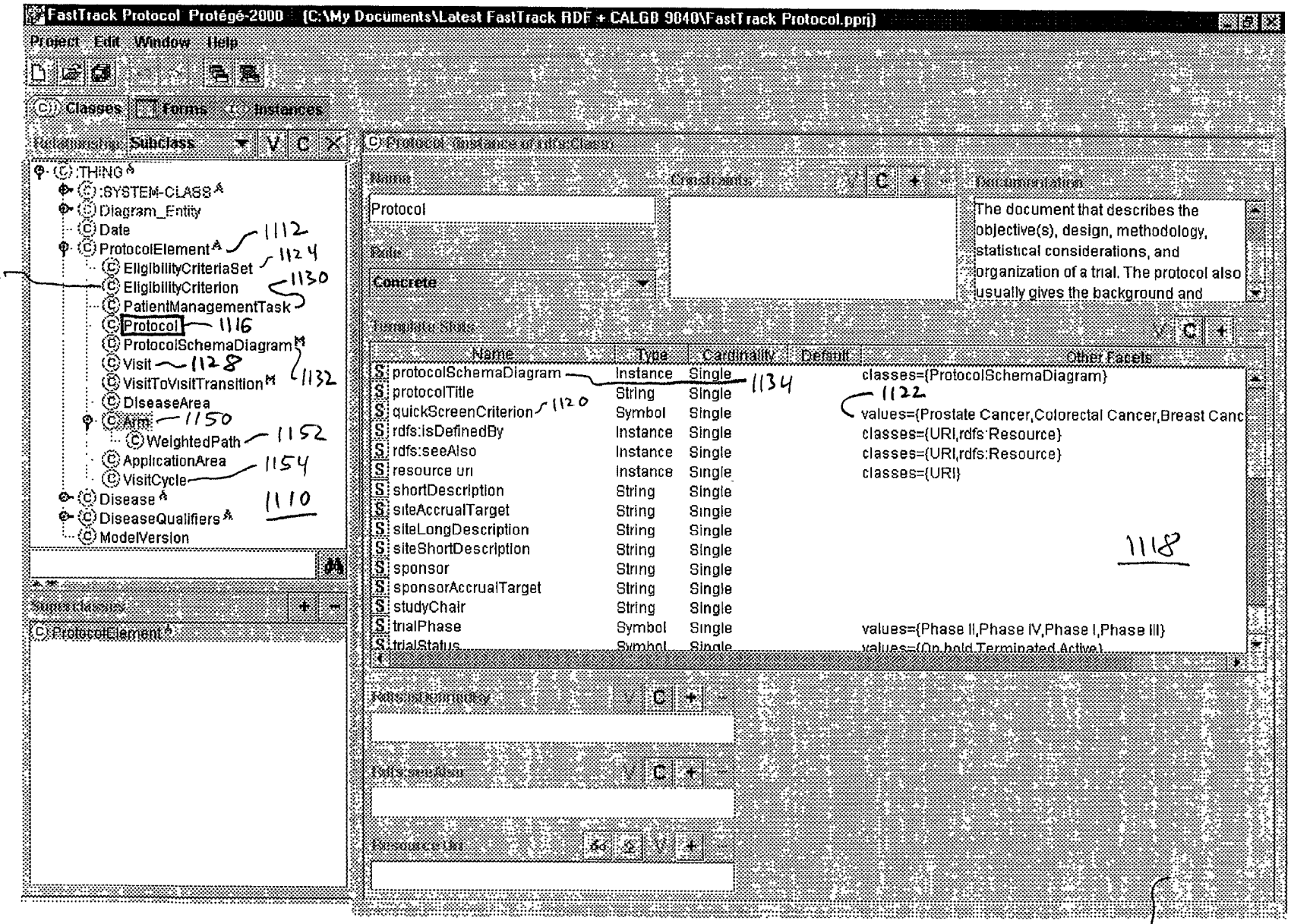

FastTrack Protocol Protégé-2000 (C:\My Documents\Latest FastTrack RDF + CALGB 9040\FastTrack Protocol.pprj)
Project Edit Window Help
Classes Forms Instances
Subclass
THING
:SYSTEM-CLASS
Diagram_Entity
Date
ProtocolElement
EligibilityCriteriaSet
EligibilityCriterion
PatientManagementTask
Protocol
ProtocolSchemaDiagram
Visit
VisitToVisitTransition
DiseaseArea
Arm
WeightedPath
ApplicationArea
VisitCycle
Disease
DiseaseQualifiers
ModelVersion
ProtocolElement
Protocol
Concrete
The document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol also usually gives the background and
Name
Type
Cardinality
Default
Other Facets
protocolSchemaDiagram Instance Single classes={ProtocolSchemaDiagram}
protocolTitle String Single
quickScreenCriterion Symbol Single values={Prostate Cancer,Colorectal Cancer,Breast Canc
rdfs:isDefinedBy Instance Single classes={URI,rdfs:Resource}
rdfs:seeAlso Instance Single classes={URI,rdfs:Resource}
resource uri Instance Single classes={URI}
shortDescription String Single
siteAccrualTarget String Single
siteLongDescription String Single
siteShortDescription String Single
sponsor String Single
sponsorAccrualTarget String Single
studyChair String Single
trialPhase Symbol Single values={Phase II,Phase IV,Phase I,Phase III}
trialStatus Symbol Single values={On hold,Terminated,Active}
1126
1112
1124
1130
1116
1128
1132
1150
1152
1154
1110
1134
1122
1120
1118
1114

Fig. 11

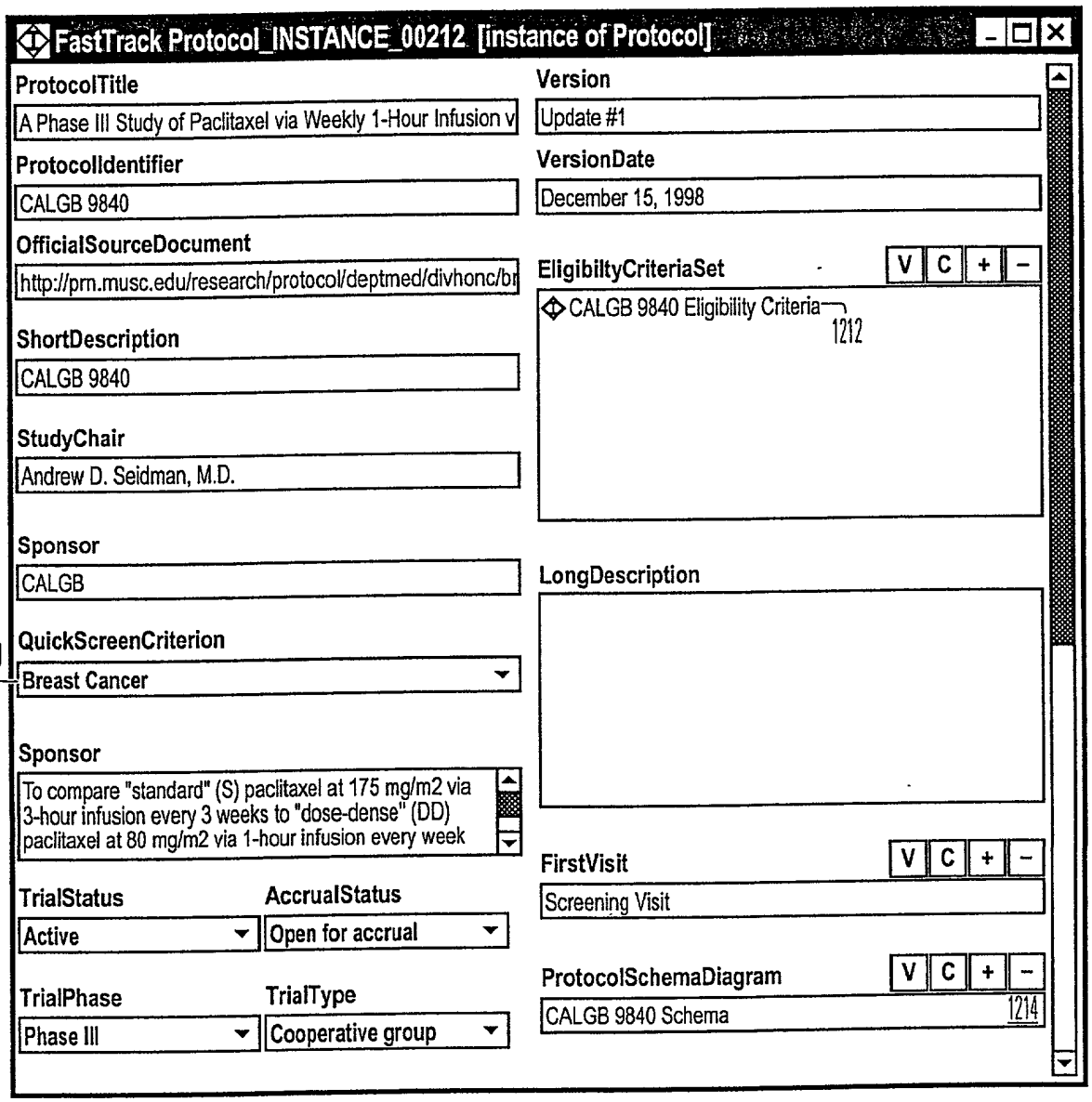

FastTrack Protocol_INSTANCE_00212 [instance of Protocol]
ProtocolTitle
A Phase III Study of Paclitaxel via Weekly 1-Hour Infusion v
ProtocolIdentifier
CALGB 9840
OfficialSourceDocument
http://prn.musc.edu/research/protocol/deptmed/divhonc/br
ShortDescription
CALGB 9840
StudyChair
Andrew D. Seidman, M.D.
Sponsor
CALGB
1210
QuickScreenCriterion
Breast Cancer
Sponsor
To compare "standard" (S) paclitaxel at 175 mg/m2 via 3-hour infusion every 3 weeks to "dose-dense" (DD) paclitaxel at 80 mg/m2 via 1-hour infusion every week
TrialStatus
Active
AccrualStatus
Open for accrual
TrialPhase
Phase III
TrialType
Cooperative group
Version
Update #1
VersionDate
December 15, 1998
EligibiltyCriteriaSet
V C + -
CALGB 9840 Eligibility Criteria
1212
LongDescription
FirstVisit
V C + -
Screening Visit
ProtocolSchemaDiagram
V C + -
CALGB 9840 Schema
1214

FIG. 12

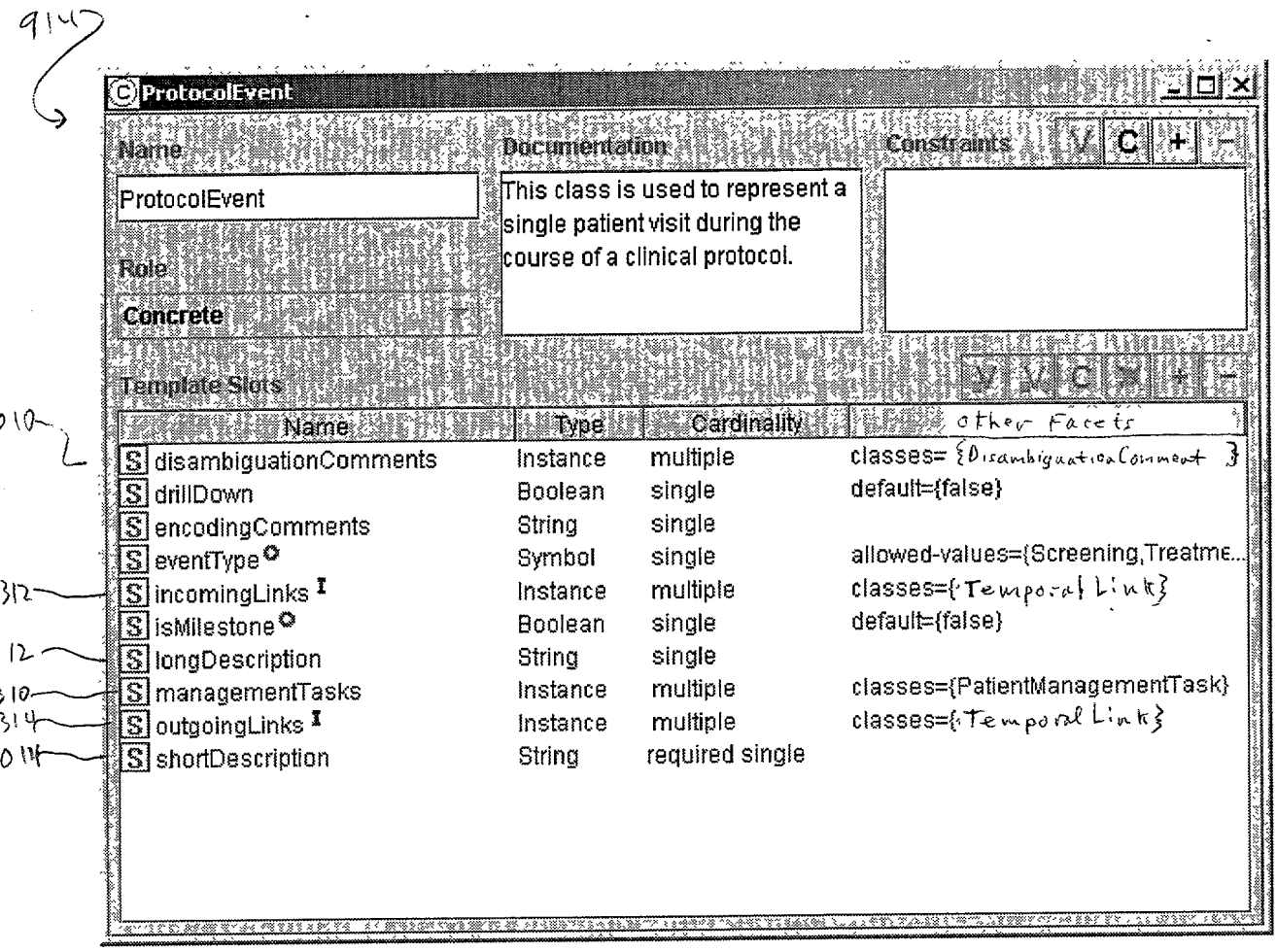

914
ProtocolEvent
Name
ProtocolEvent
Documentation
This class is used to represent a single patient visit during the course of a clinical protocol.
Constraints
Role
Concrete
Template Slots
1010
Name
Type
Cardinality
other Facets
disambiguationComments
Instance
multiple
classes={DisambiguationComment}
drillDown
Boolean
single
default={false}
encodingComments
String
single
eventType
Symbol
single
allowed-values={Screening,Treatme...
1312
incomingLinks
Instance
multiple
classes={TemporalLink}
isMilestone
Boolean
single
default={false}
1012
longDescription
String
single
1310
managementTasks
Instance
multiple
classes={PatientManagementTask}
1314
outgoingLinks
Instance
multiple
classes={TemporalLink}
1014
shortDescription
String
required single

Fig. 13

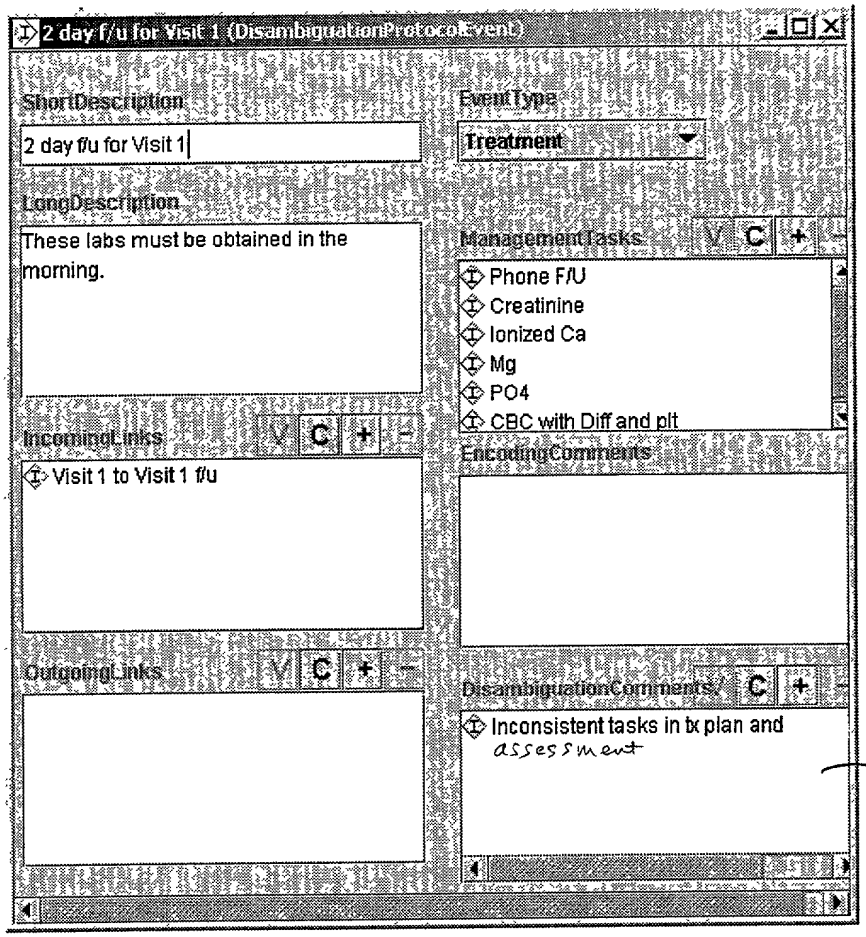

2 day f/u for Visit 1 (DisambiguationProtocolEvent)
ShortDescription
2 day f/u for Visit 1
EventType
Treatment
LongDescription
These labs must be obtained in the morning.
ManagementTasks
Phone F/U
Creatinine
Ionized Ca
Mg
PO4
CBC with Diff and plt
IncomingLinks
Visit 1 to Visit 1 f/u
EncodingComments
OutgoingLinks
DisambiguationComments
Inconsistent tasks in tx plan and assessment
1410

Fig. 14

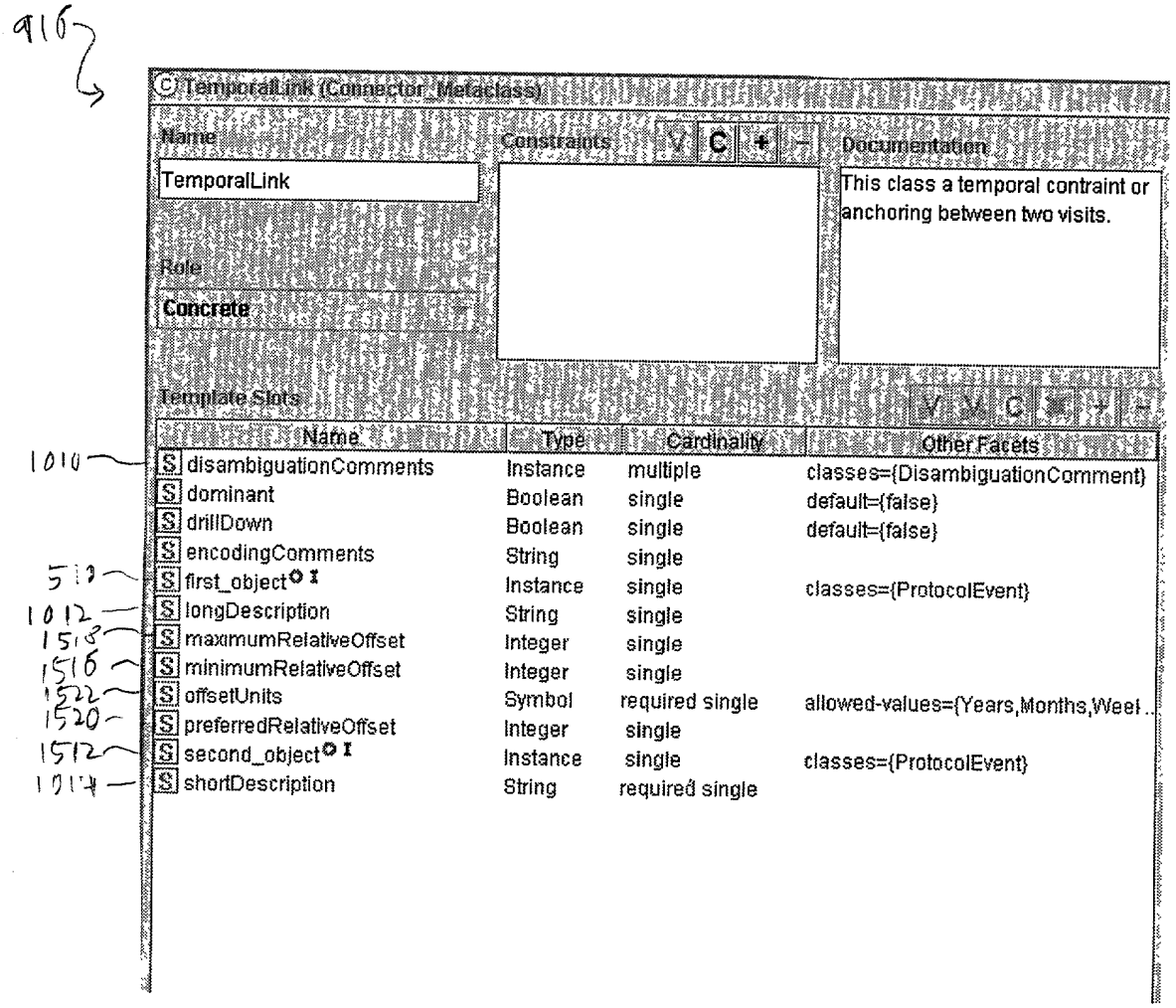

916
TemporalLink (Connector_Metaclass)
Name
TemporalLink
Role
Concrete
Constraints
Documentation
This class a temporal contraint or anchoring between two visits.
Template Slots
Name
Type
Cardinality
Other Facets
1010
disambiguationComments
Instance
multiple
classes={DisambiguationComment}
dominant
Boolean
single
default={false}
drillDown
Boolean
single
default={false}
encodingComments
String
single
510
first_object
Instance
single
classes={ProtocolEvent}
1012
longDescription
String
single
1518
maximumRelativeOffset
Integer
single
1516
minimumRelativeOffset
Integer
single
1522
offsetUnits
Symbol
required single
allowed-values={Years,Months,Weel
1520
preferredRelativeOffset
Integer
single
1512
second_object
Instance
single
classes={ProtocolEvent}
1014
shortDescription
String
required single

Fig. 15

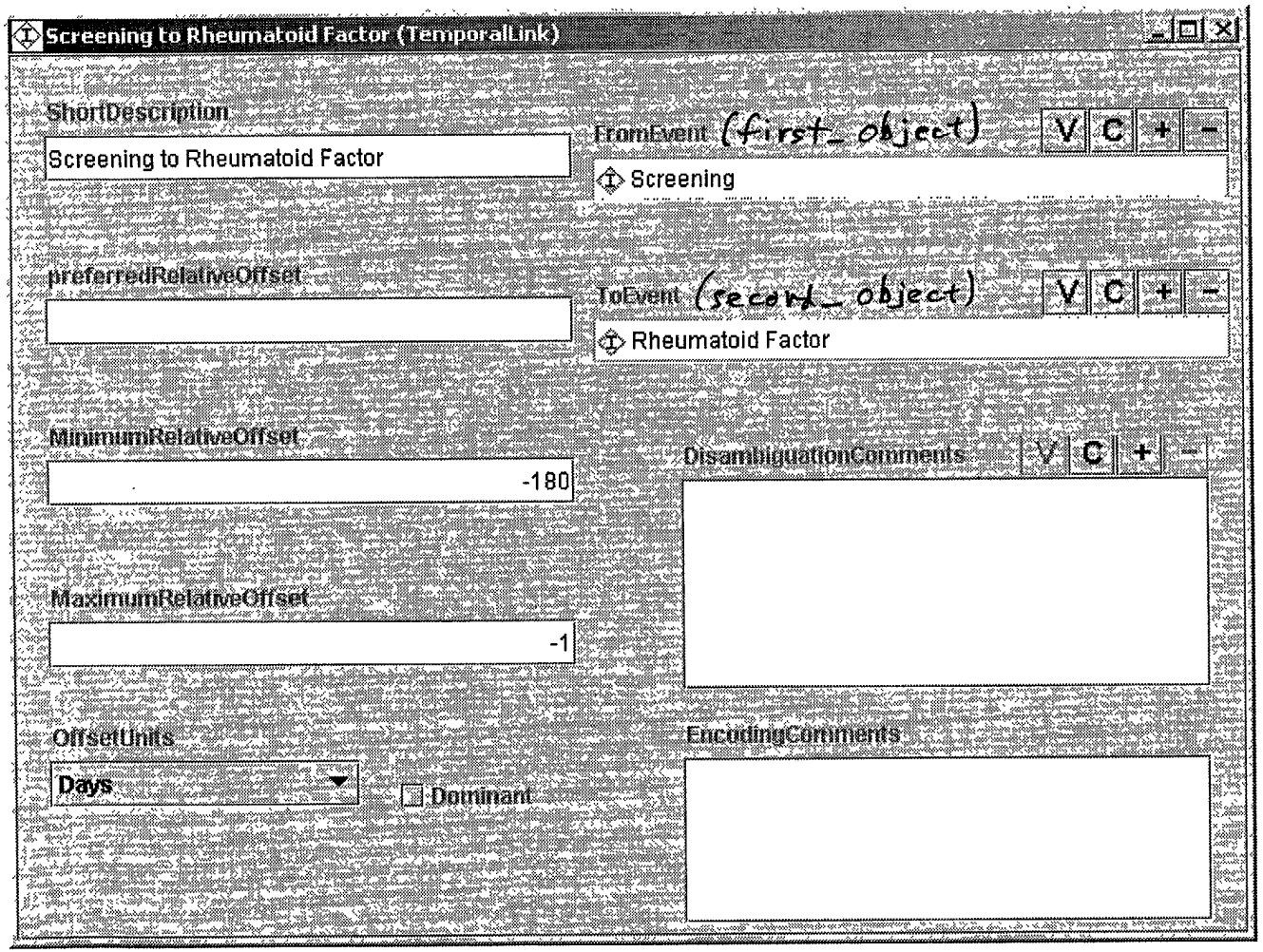


Fig. 16

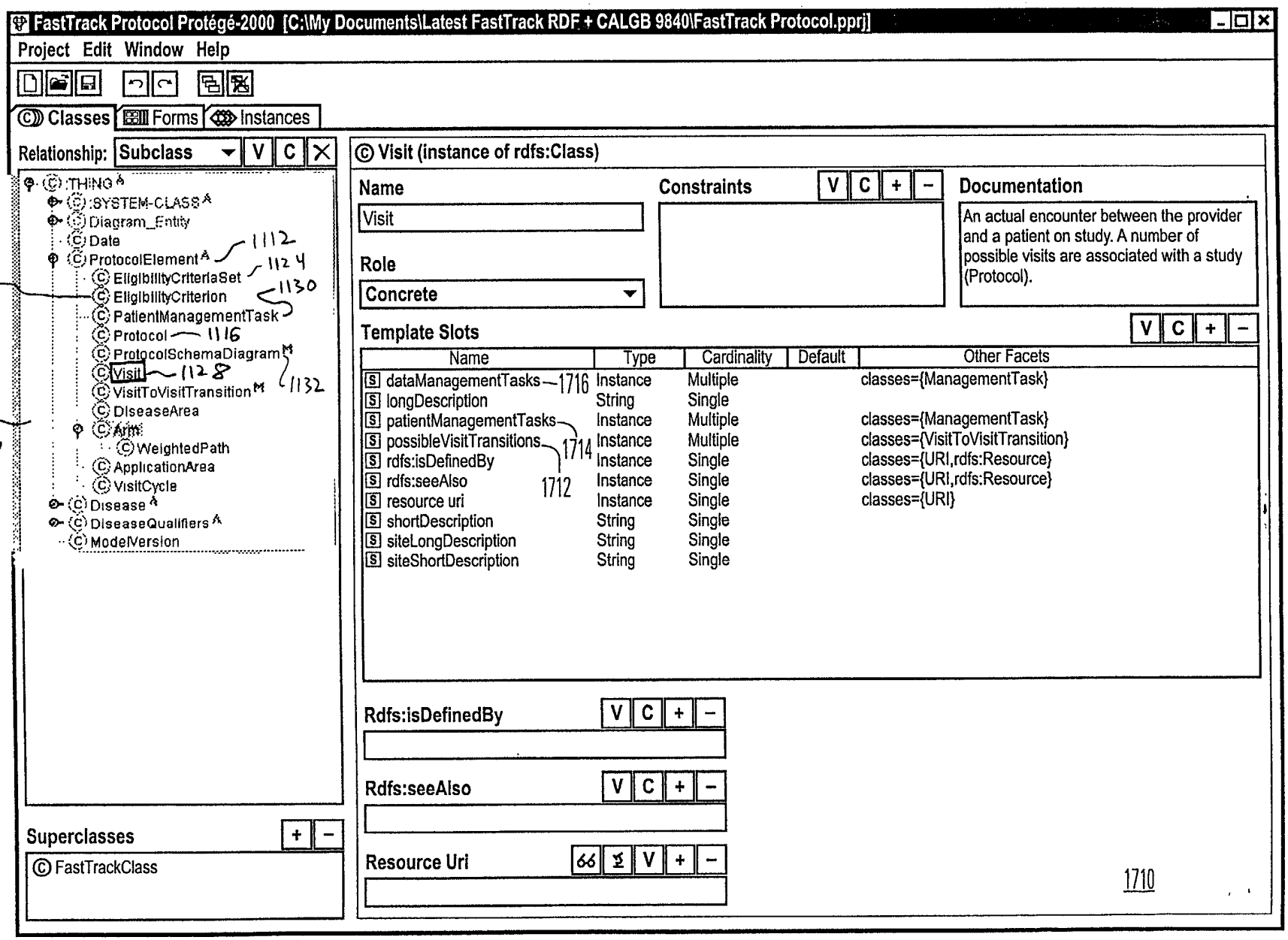

FastTrack Protocol Protégé-2000 [C:\My Documents\Latest FastTrack RDF + CALGB 9840\FastTrack Protocol.pprj]
Project Edit Window Help
Classes Forms Instances
Relationship: Subclass V C
THING
:SYSTEM-CLASS
Diagram_Entity
Date
ProtocolElement
EligibilityCriteriaSet
EligibilityCriterion
PatientManagementTask
Protocol
ProtocolSchemaDiagram
Visit
VisitToVisitTransition
DiseaseArea
Arm
WeightedPath
ApplicationArea
VisitCycle
Disease
DiseaseQualifiers
ModelVersion
1112
1114
1126
1130
1116
1128
1132
1110
Superclasses
FastTrackClass
Visit (instance of rdfs:Class)
Name
Visit
Role
Concrete
Constraints
Documentation
An actual encounter between the provider and a patient on study. A number of possible visits are associated with a study (Protocol).
Template Slots
Name | Type | Cardinality | Default | Other Facets
dataManagementTasks | Instance | Multiple | classes={ManagementTask}
longDescription | String | Single
patientManagementTasks | Instance | Multiple | classes={ManagementTask}
possibleVisitTransitions | Instance | Multiple | classes={VisitToVisitTransition}
rdfs:isDefinedBy | Instance | Single | classes={URI,rdfs:Resource}
rdfs:seeAlso | Instance | Single | classes={URI,rdfs:Resource}
resource uri | Instance | Single | classes={URI}
shortDescription | String | Single
siteLongDescription | String | Single
siteShortDescription | String | Single
1716
1714
1712
Rdfs:isDefinedBy
Rdfs:seeAlso
Resource Uri
1710

FIG. 17

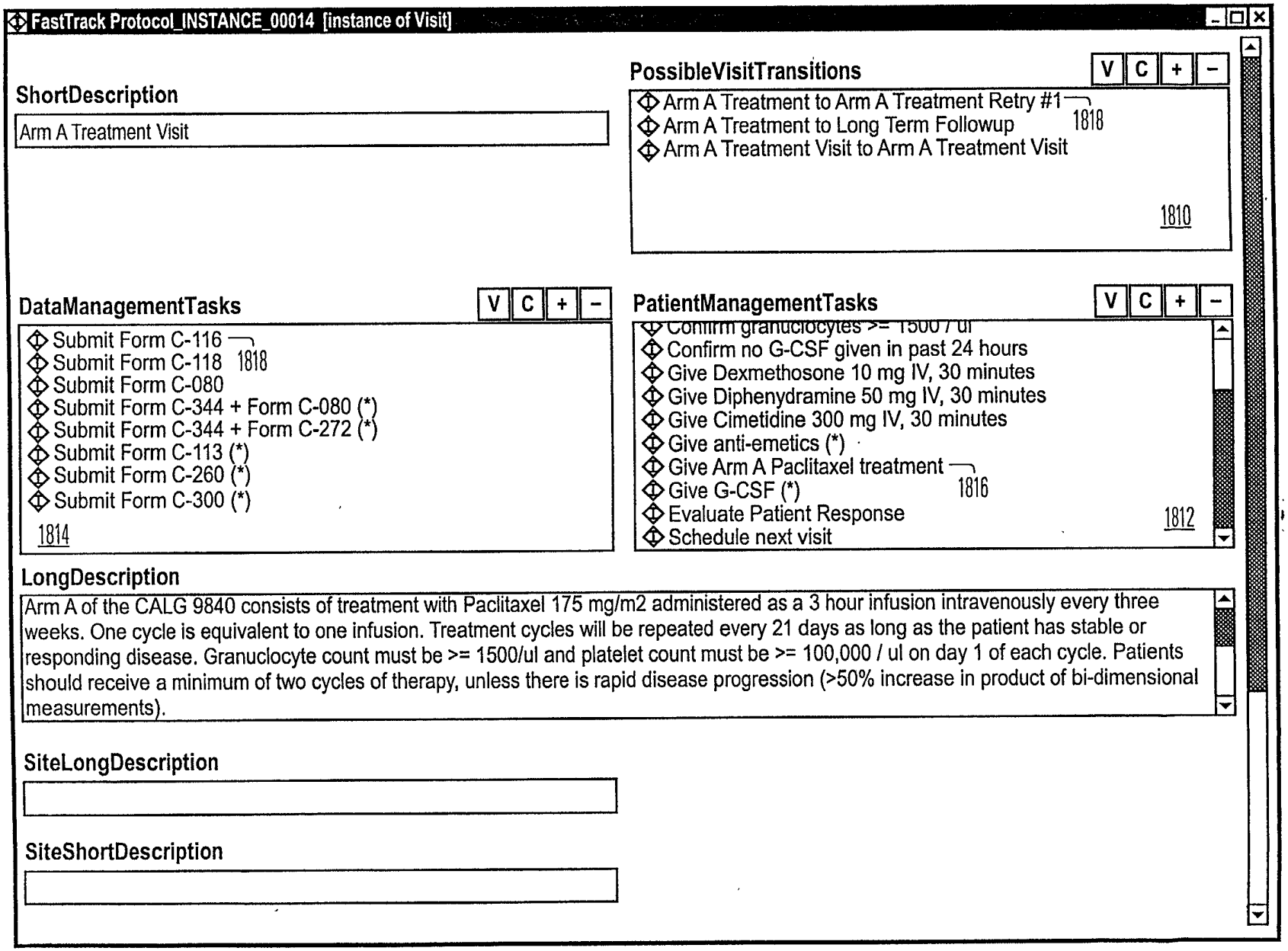

FastTrack Protocol_INSTANCE_00014 [instance of Visit]
ShortDescription
Arm A Treatment Visit
PossibleVisitTransitions
V C + −
Arm A Treatment to Arm A Treatment Retry #1
Arm A Treatment to Long Term Followup
Arm A Treatment Visit to Arm A Treatment Visit
1818
1810
DataManagementTasks
V C + −
Submit Form C-116
Submit Form C-118
Submit Form C-080
Submit Form C-344 + Form C-080 (*)
Submit Form C-344 + Form C-272 (*)
Submit Form C-113 (*)
Submit Form C-260 (*)
Submit Form C-300 (*)
1818
1814
PatientManagementTasks
V C + −
Confirm granulocytes >= 1500 / ul
Confirm no G-CSF given in past 24 hours
Give Dexmethosone 10 mg IV, 30 minutes
Give Diphenydramine 50 mg IV, 30 minutes
Give Cimetidine 300 mg IV, 30 minutes
Give anti-emetics (*)
Give Arm A Paclitaxel treatment
Give G-CSF (*)
Evaluate Patient Response
Schedule next visit
1816
1812
LongDescription
Arm A of the CALG 9840 consists of treatment with Paclitaxel 175 mg/m2 administered as a 3 hour infusion intravenously every three weeks. One cycle is equivalent to one infusion. Treatment cycles will be repeated every 21 days as long as the patient has stable or responding disease. Granuclocyte count must be >= 1500/ul and platelet count must be >= 100,000 / ul on day 1 of each cycle. Patients should receive a minimum of two cycles of therapy, unless there is rapid disease progression (>50% increase in product of bi-dimensional measurements).
SiteLongDescription
SiteShortDescription

FIG. 18

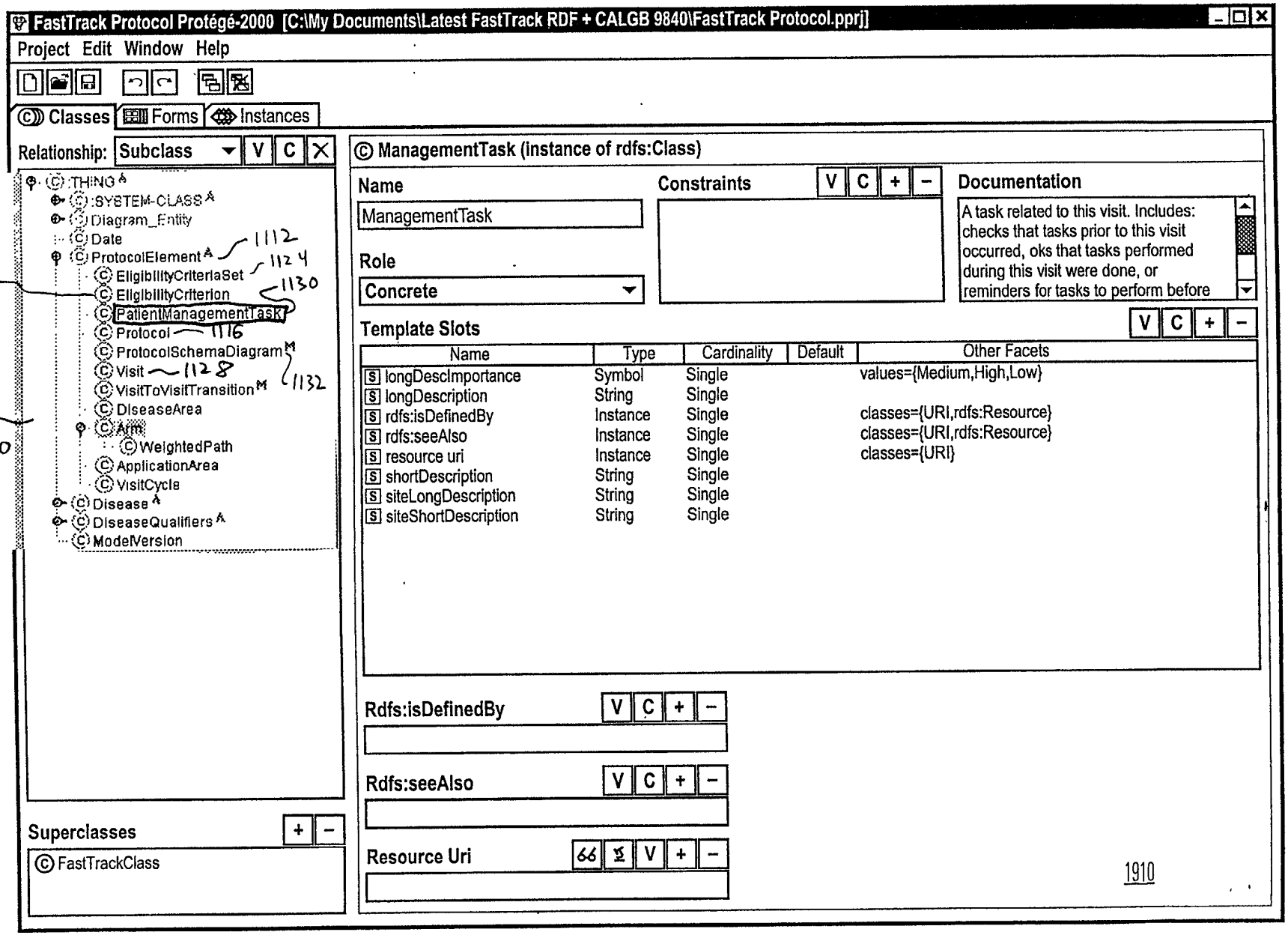


FIG. 19

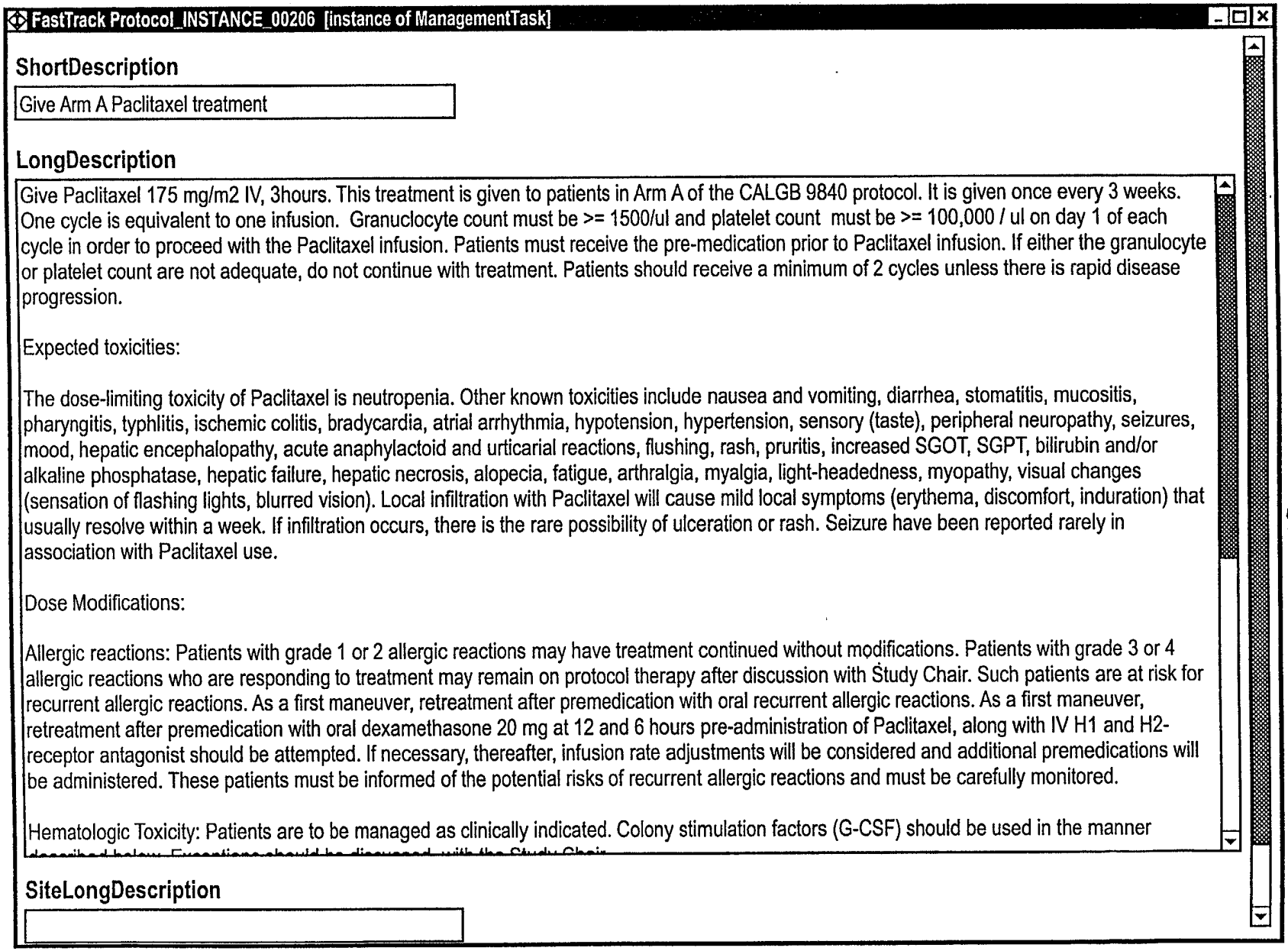

FastTrack Protocol_INSTANCE_00206 [instance of ManagementTask]
ShortDescription
Give Arm A Paclitaxel treatment
LongDescription
Give Paclitaxel 175 mg/m2 IV, 3hours. This treatment is given to patients in Arm A of the CALGB 9840 protocol. It is given once every 3 weeks. One cycle is equivalent to one infusion. Granuclocyte count must be >= 1500/ul and platelet count must be >= 100,000 / ul on day 1 of each cycle in order to proceed with the Paclitaxel infusion. Patients must receive the pre-medication prior to Paclitaxel infusion. If either the granulocyte or platelet count are not adequate, do not continue with treatment. Patients should receive a minimum of 2 cycles unless there is rapid disease progression.
Expected toxicities:
The dose-limiting toxicity of Paclitaxel is neutropenia. Other known toxicities include nausea and vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, bradycardia, atrial arrhythmia, hypotension, hypertension, sensory (taste), peripheral neuropathy, seizures, mood, hepatic encephalopathy, acute anaphylactoid and urticarial reactions, flushing, rash, pruritis, increased SGOT, SGPT, bilirubin and/or alkaline phosphatase, hepatic failure, hepatic necrosis, alopecia, fatigue, arthralgia, myalgia, light-headedness, myopathy, visual changes (sensation of flashing lights, blurred vision). Local infiltration with Paclitaxel will cause mild local symptoms (erythema, discomfort, induration) that usually resolve within a week. If infiltration occurs, there is the rare possibility of ulceration or rash. Seizure have been reported rarely in association with Paclitaxel use.
Dose Modifications:
Allergic reactions: Patients with grade 1 or 2 allergic reactions may have treatment continued without modifications. Patients with grade 3 or 4 allergic reactions who are responding to treatment may remain on protocol therapy after discussion with Study Chair. Such patients are at risk for recurrent allergic reactions. As a first maneuver, retreatment after premedication with oral recurrent allergic reactions. As a first maneuver, retreatment after premedication with oral dexamethasone 20 mg at 12 and 6 hours pre-administration of Paclitaxel, along with IV H1 and H2-receptor antagonist should be attempted. If necessary, thereafter, infusion rate adjustments will be considered and additional premedications will be administered. These patients must be informed of the potential risks of recurrent allergic reactions and must be carefully monitored.
Hematologic Toxicity: Patients are to be managed as clinically indicated. Colony stimulation factors (G-CSF) should be used in the manner
SiteLongDescription

FIG. 20

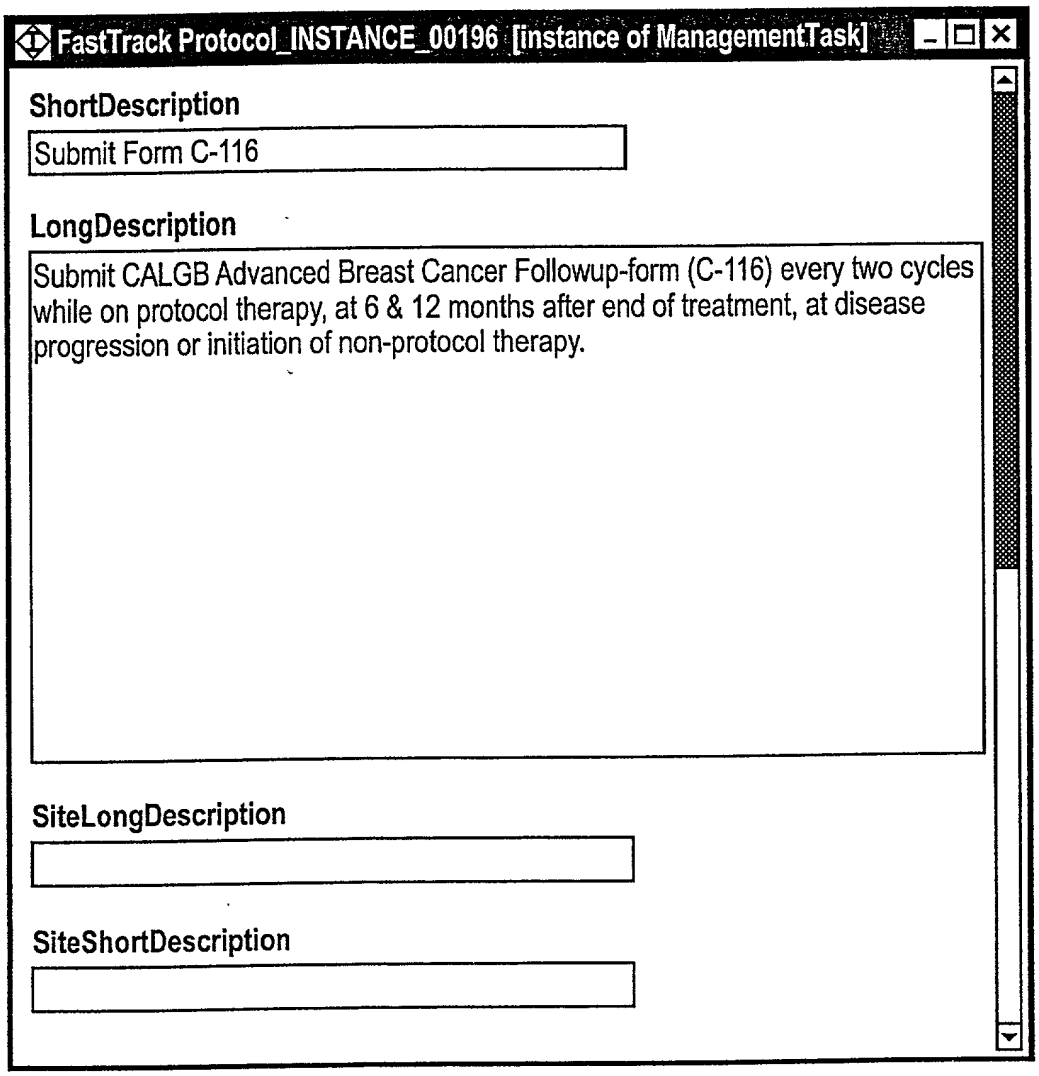

FastTrack Protocol_INSTANCE_00196 [instance of ManagementTask]
ShortDescription
Submit Form C-116
LongDescription
Submit CALGB Advanced Breast Cancer Followup-form (C-116) every two cycles while on protocol therapy, at 6 & 12 months after end of treatment, at disease progression or initiation of non-protocol therapy.
SiteLongDescription
SiteShortDescription

FIG. 21

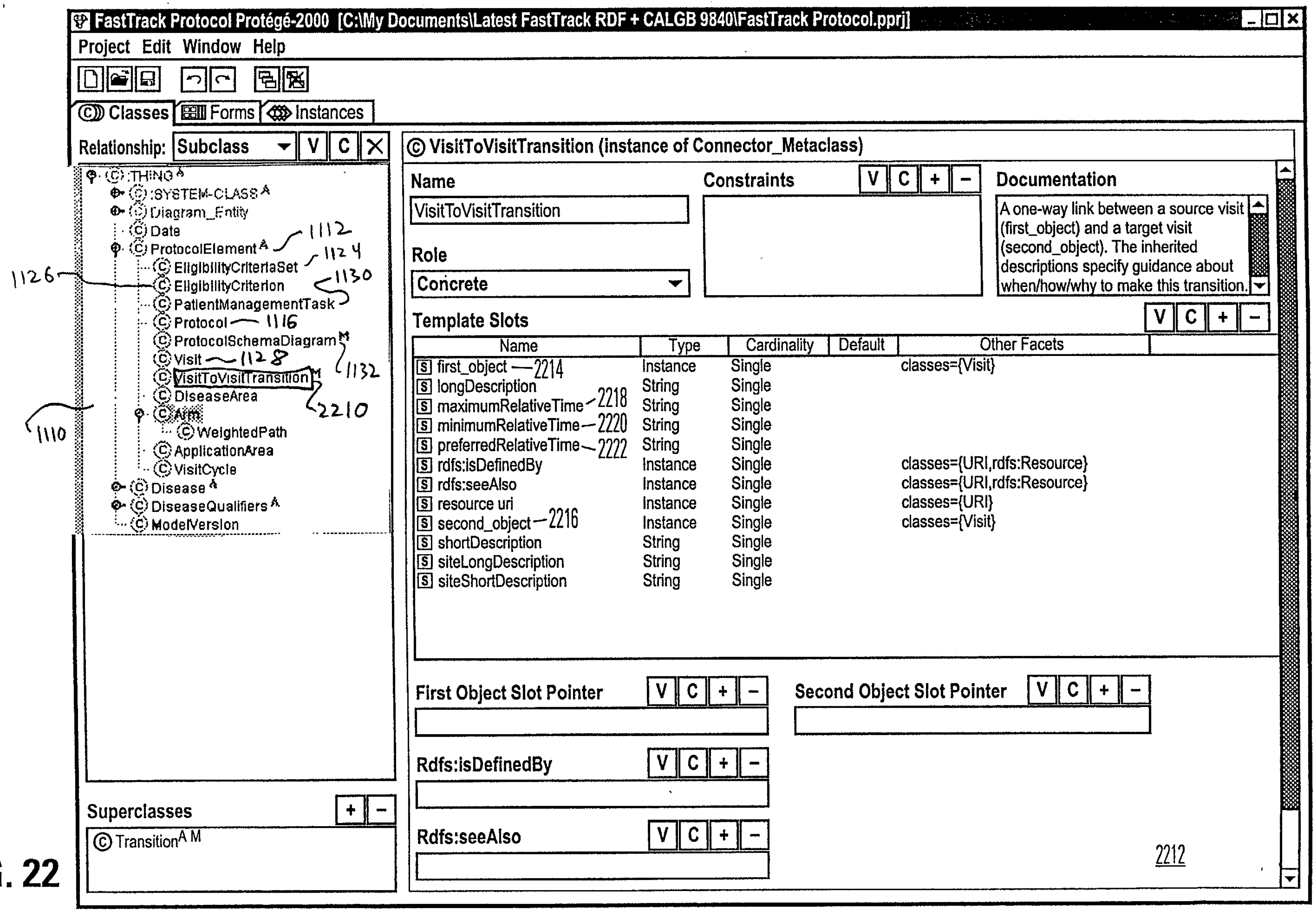

FastTrack Protocol Protégé-2000 [C:\My Documents\Latest FastTrack RDF + CALGB 9840\FastTrack Protocol.pprj]
Project Edit Window Help
Classes Forms Instances
Relationship: Subclass V C
:THING
:SYSTEM-CLASS
Diagram_Entity
Date
ProtocolElement
EligibilityCriteriaSet
EligibilityCriterion
PatientManagementTask
Protocol
ProtocolSchemaDiagram
Visit
VisitToVisitTransition
DiseaseArea
Arm
WeightedPath
ApplicationArea
VisitCycle
Disease
DiseaseQualifiers
ModelVersion
Superclasses
Transition
1110
1112
1116
1124
1126
1128
1130
1132
2210
VisitToVisitTransition (instance of Connector_Metaclass)
Name
VisitToVisitTransition
Constraints
Documentation
A one-way link between a source visit (first_object) and a target visit (second_object). The inherited descriptions specify guidance about when/how/why to make this transition.
Role
Concrete
Template Slots
Name Type Cardinality Default Other Facets
first_object — 2214 Instance Single classes={Visit}
longDescription String Single
maximumRelativeTime — 2218 String Single
minimumRelativeTime — 2220 String Single
preferredRelativeTime — 2222 String Single
rdfs:isDefinedBy Instance Single classes={URI,rdfs:Resource}
rdfs:seeAlso Instance Single classes={URI,rdfs:Resource}
resource uri Instance Single classes={URI}
second_object — 2216 Instance Single classes={Visit}
shortDescription String Single
siteLongDescription String Single
siteShortDescription String Single
First Object Slot Pointer
Second Object Slot Pointer
Rdfs:isDefinedBy
Rdfs:seeAlso
2212

FIG. 22

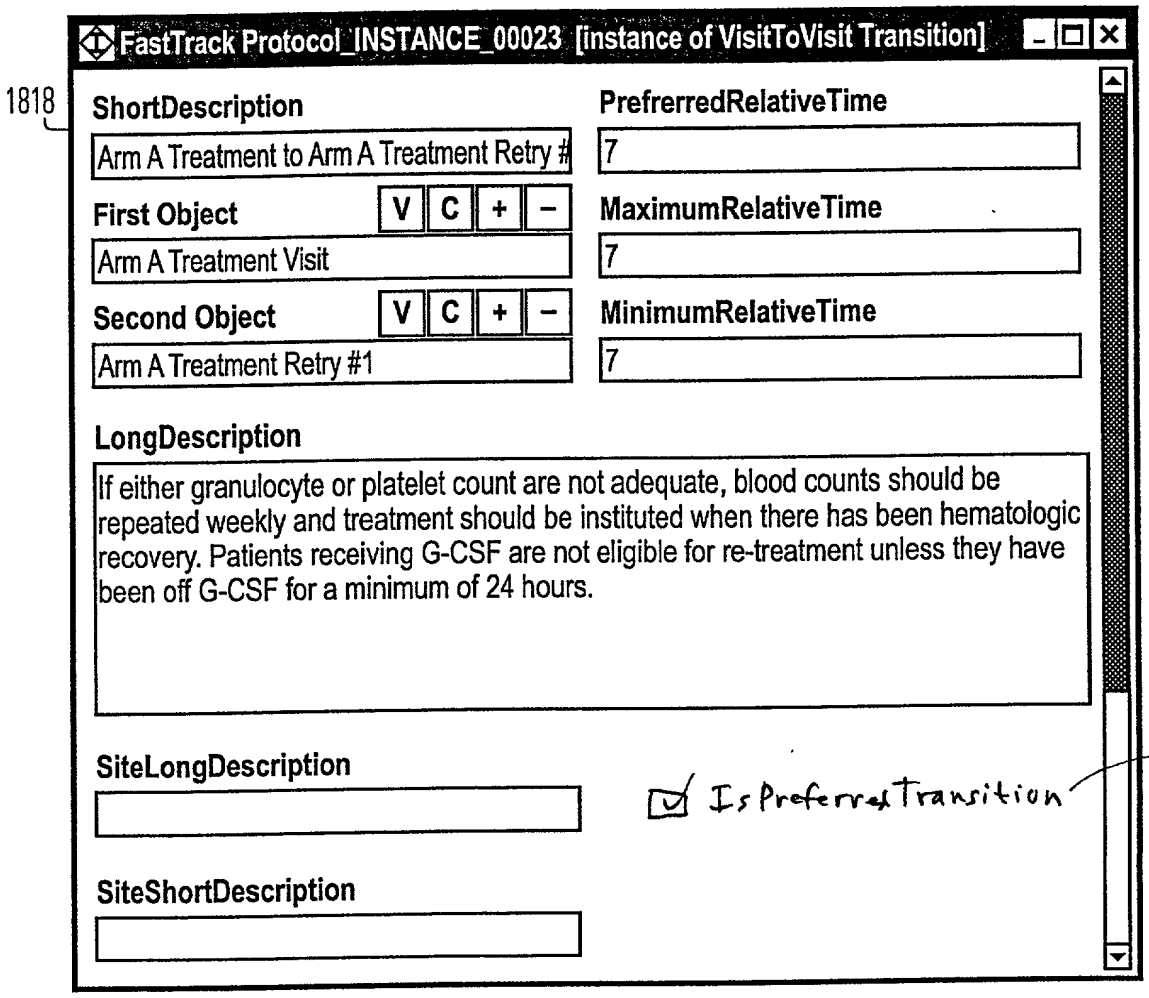

FastTrack Protocol_INSTANCE_00023 [instance of VisitToVisit Transition]
1818
ShortDescription
Arm A Treatment to Arm A Treatment Retry #
PrefrerredRelativeTime
7
First Object
V
C
+
−
Arm A Treatment Visit
MaximumRelativeTime
7
Second Object
V
C
+
−
Arm A Treatment Retry #1
MinimumRelativeTime
7
LongDescription
If either granulocyte or platelet count are not adequate, blood counts should be repeated weekly and treatment should be instituted when there has been hematologic recovery. Patients receiving G-CSF are not eligible for re-treatment unless they have been off G-CSF for a minimum of 24 hours.
SiteLongDescription
IsPreferredTransition
2310
SiteShortDescription

FIG. 23

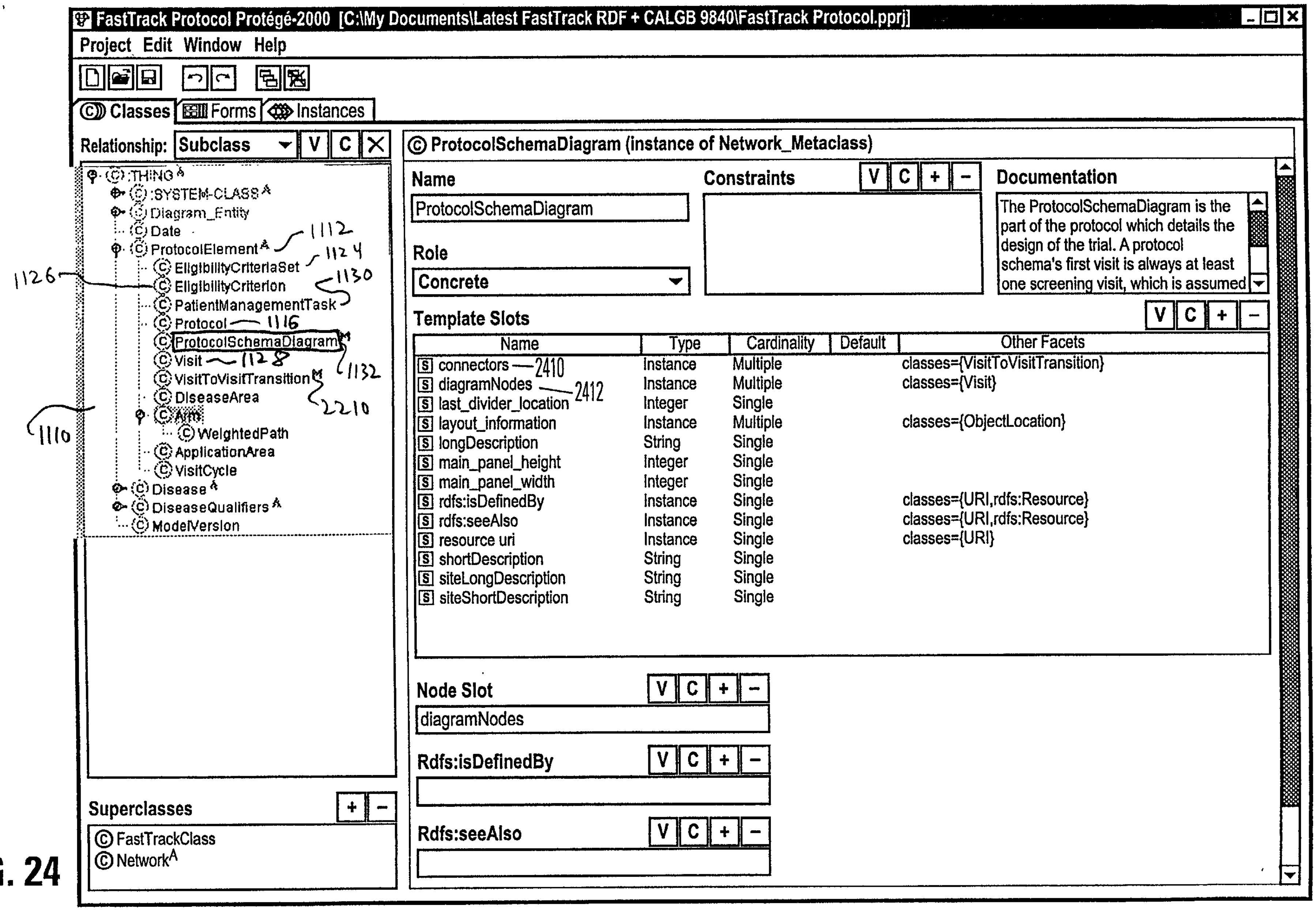

FastTrack Protocol Protégé-2000 [C:\My Documents\Latest FastTrack RDF + CALGB 9840\FastTrack Protocol.pprj]
Project Edit Window Help
Classes Forms Instances
Relationship: Subclass V C X
:THING
:SYSTEM-CLASS
Diagram_Entity
Date
ProtocolElement
EligibilityCriteriaSet
EligibilityCriterion
PatientManagementTask
Protocol
ProtocolSchemaDiagram
Visit
VisitToVisitTransition
DiseaseArea
Arm
WeightedPath
ApplicationArea
VisitCycle
Disease
DiseaseQualifiers
ModelVersion
1112
1124
1126
1130
1116
1128
1132
2210
1110
Superclasses
FastTrackClass
Network
ProtocolSchemaDiagram (instance of Network_Metaclass)
Name
ProtocolSchemaDiagram
Constraints
Documentation
The ProtocolSchemaDiagram is the part of the protocol which details the design of the trial. A protocol schema's first visit is always at least one screening visit, which is assumed
Role
Concrete
Template Slots
Name Type Cardinality Default Other Facets
connectors Instance Multiple classes={VisitToVisitTransition}
diagramNodes Instance Multiple classes={Visit}
last_divider_location Integer Single
layout_information Instance Multiple classes={ObjectLocation}
longDescription String Single
main_panel_height Integer Single
main_panel_width Integer Single
rdfs:isDefinedBy Instance Single classes={URI,rdfs:Resource}
rdfs:seeAlso Instance Single classes={URI,rdfs:Resource}
resource uri Instance Single classes={URI}
shortDescription String Single
siteLongDescription String Single
siteShortDescription String Single
2410
2412
Node Slot
diagramNodes
Rdfs:isDefinedBy
Rdfs:seeAlso

FIG. 24

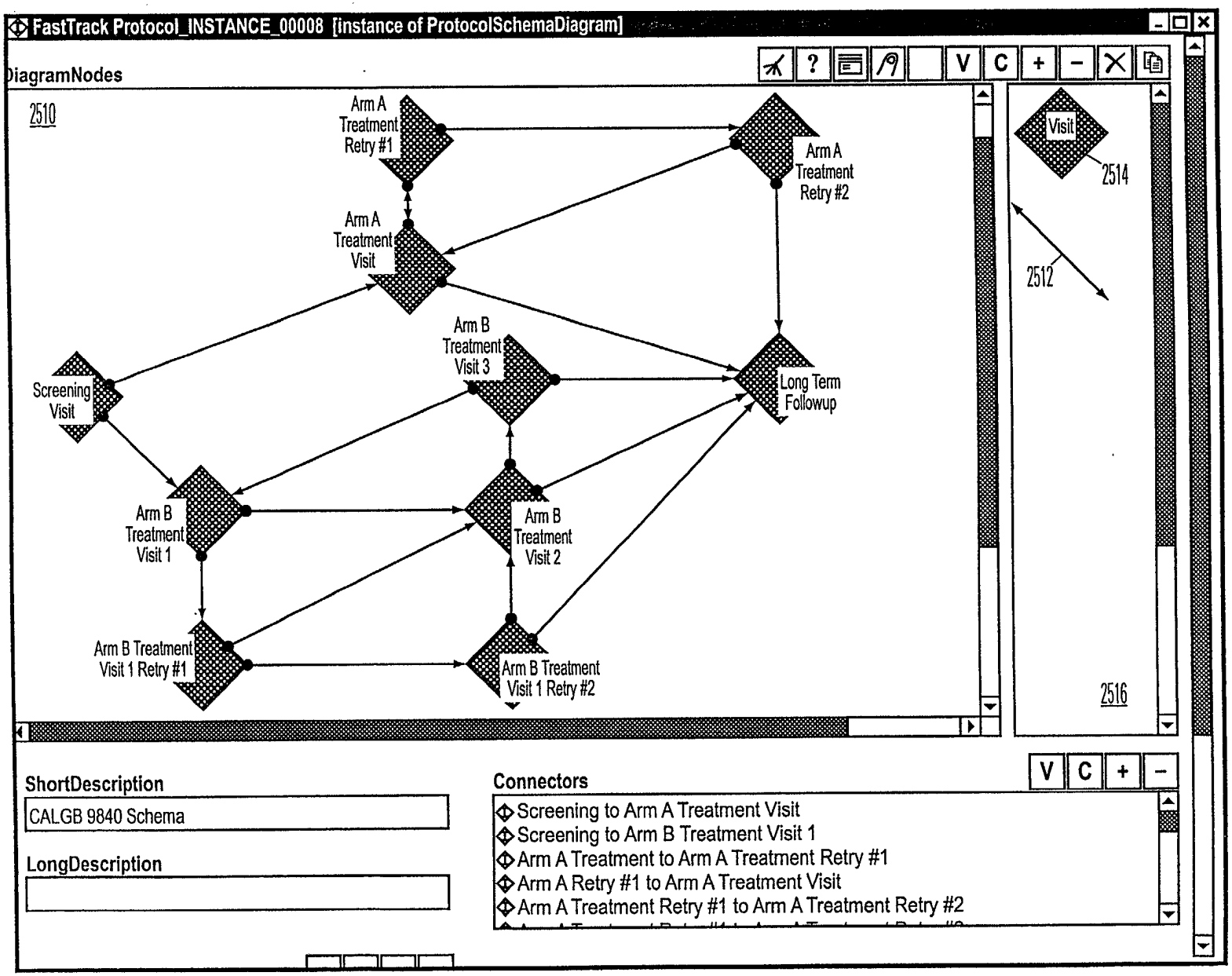


FIG. 25

940

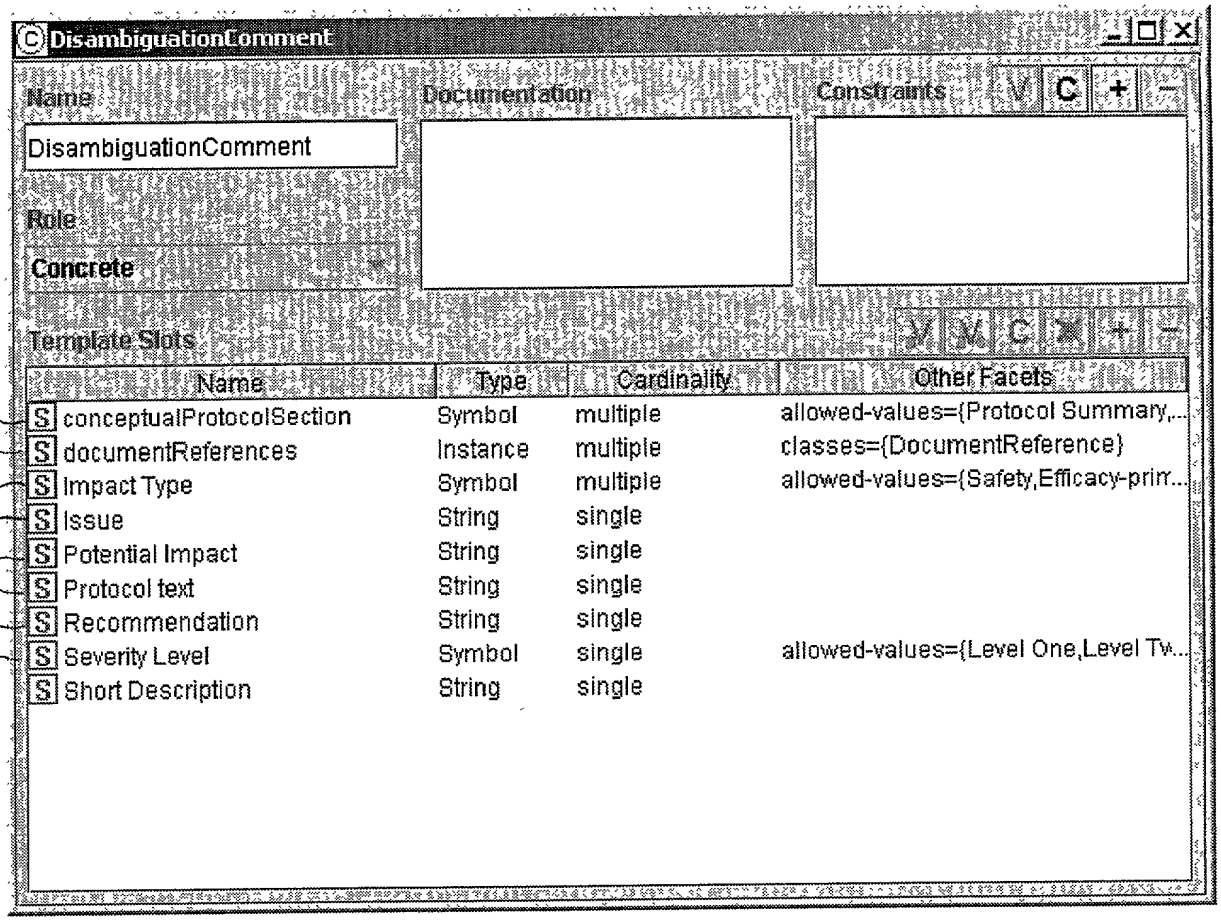


Fig. 26

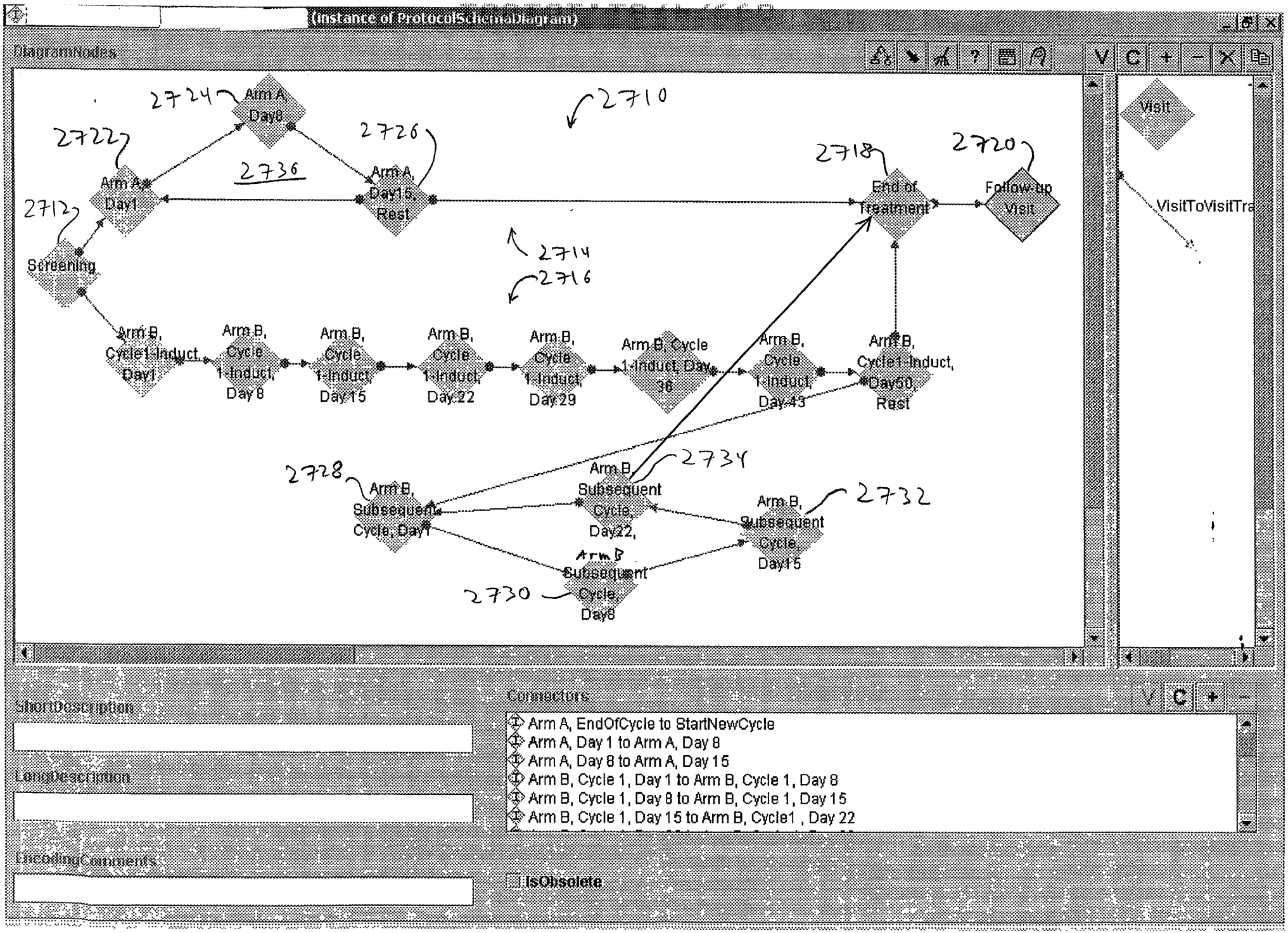

(Instance of ProtocolSchemaDiagram)
Diagramnodes:
2724
Arm A, Day8
2710
2722
2726
2736
Arm A, Day1
Arm A, Day15, Rest
2718
2720
End of Treatment
Follow-up Visit
2712
Screening
2714
2716
Arm B, Cycle1-Induct, Day1
Arm B, Cycle 1-Induct, Day 8
Arm B, Cycle 1-Induct, Day 15
Arm B, Cycle 1-Induct, Day 22
Arm B, Cycle 1-Induct, Day 29
Arm B, Cycle 1-Induct, Day 36
Arm B, Cycle 1-Induct, Day 43
Arm B, Cycle1-Induct, Day50, Rest
2728
2734
Arm B, Subsequent Cycle, Day1
Arm B, Subsequent Cycle, Day22,
Arm B, Subsequent Cycle, Day15
2732
Arm B Subsequent Cycle, Day8
2730
Visit
VisitToVisitTra
ShortDescription:
LongDescription:
EncodingComments:
Connections:
Arm A, EndOfCycle to StartNewCycle
Arm A, Day 1 to Arm A, Day 8
Arm A, Day 8 to Arm A, Day 15
Arm B, Cycle 1, Day 1 to Arm B, Cycle 1, Day 8
Arm B, Cycle 1, Day 8 to Arm B, Cycle 1, Day 15
Arm B, Cycle 1, Day 15 to Arm B, Cycle1 , Day 22
IsObsolete

Fig. 27

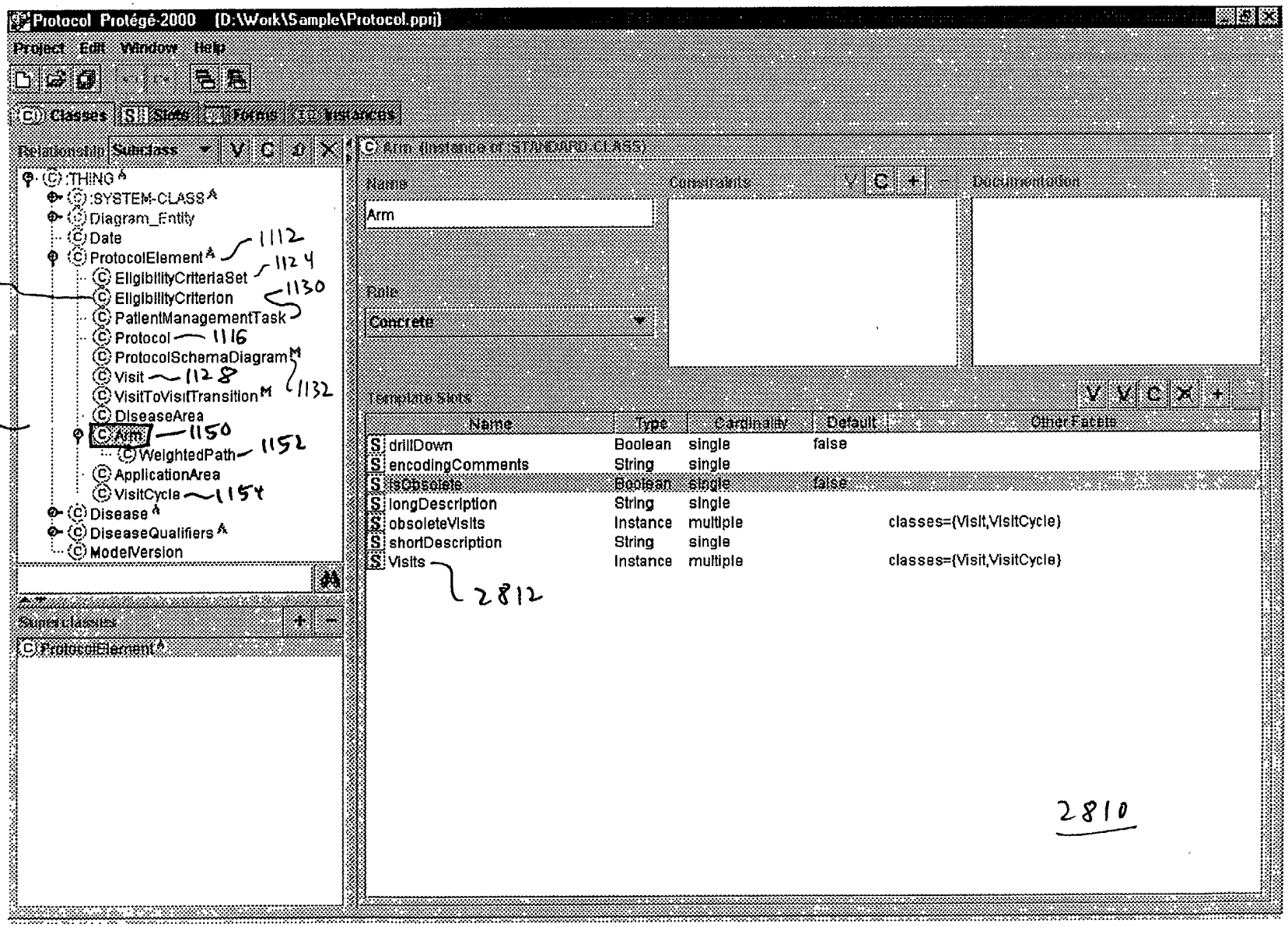


Fig. 28

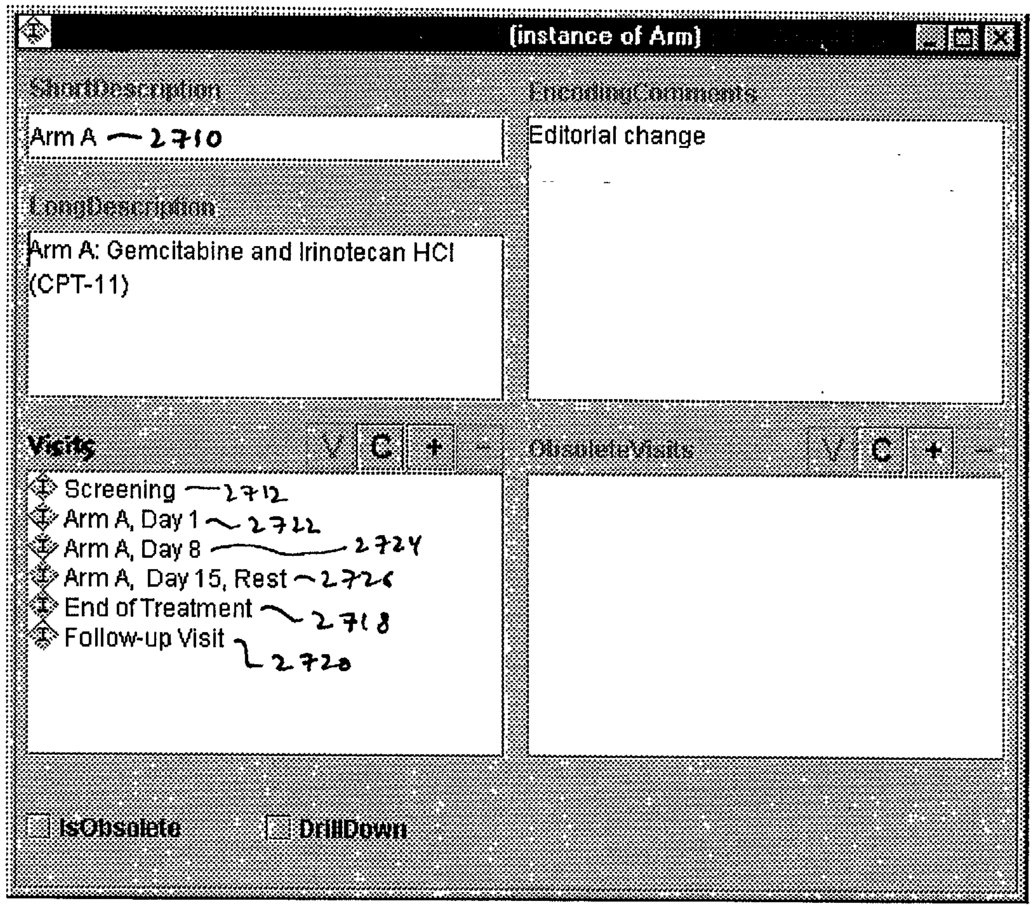

(instance of Arm)
ShortDescription
Arm A
2710
EncodingComments
Editorial change
LongDescription
Arm A: Gemcitabine and Irinotecan HCl (CPT-11)
Visits
V C + -
Screening
2712
Arm A, Day 1
2722
Arm A, Day 8
2724
Arm A, Day 15, Rest
2726
End of Treatment
2718
Follow-up Visit
2720
ObsoleteVisits
V C + -
IsObsolete
DrillDown

Fig. 29

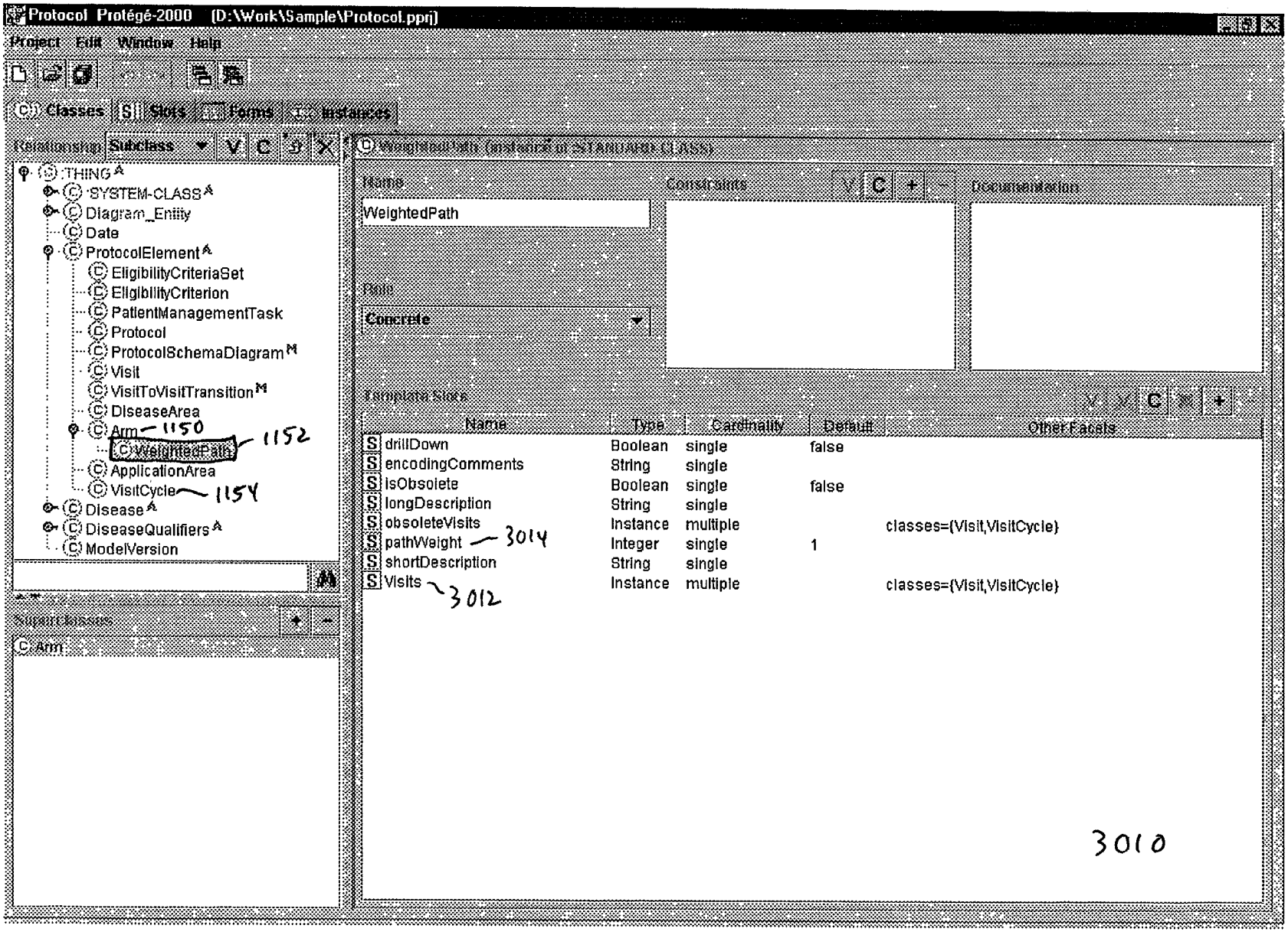


Fig. 30

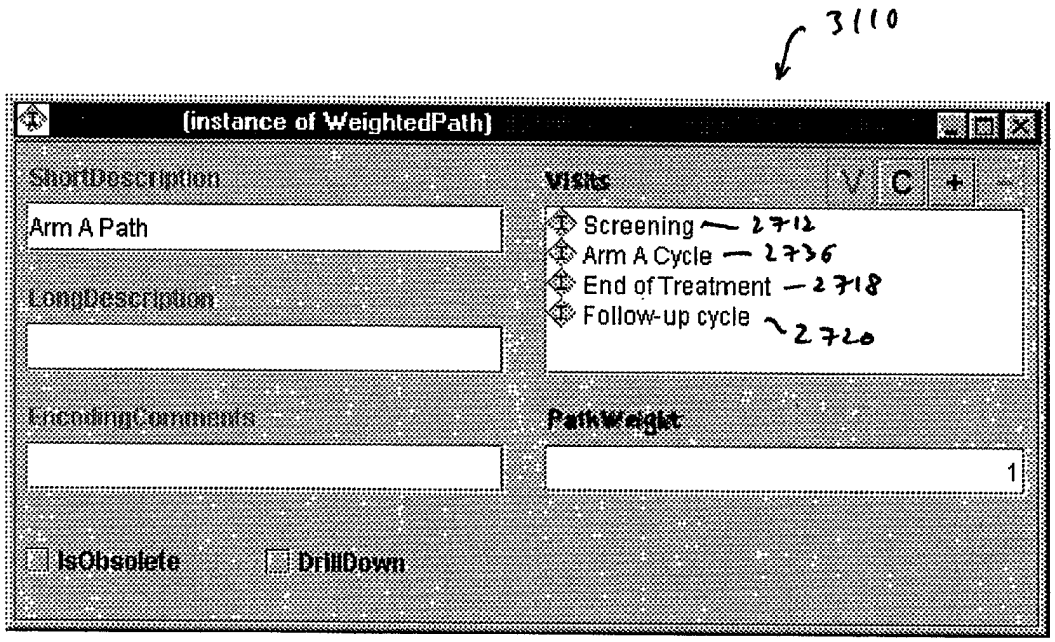


Fig. 31

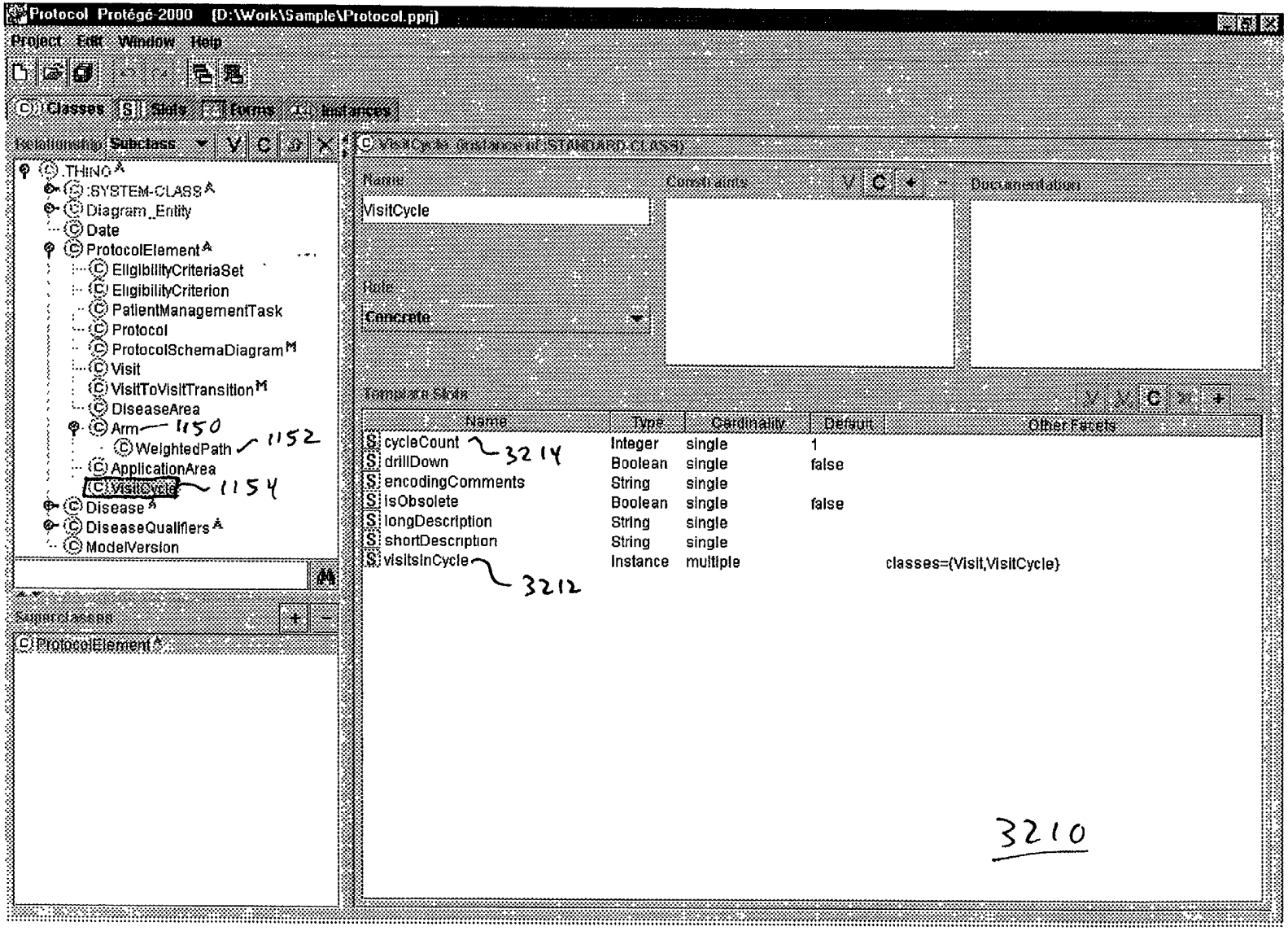


Fig. 32

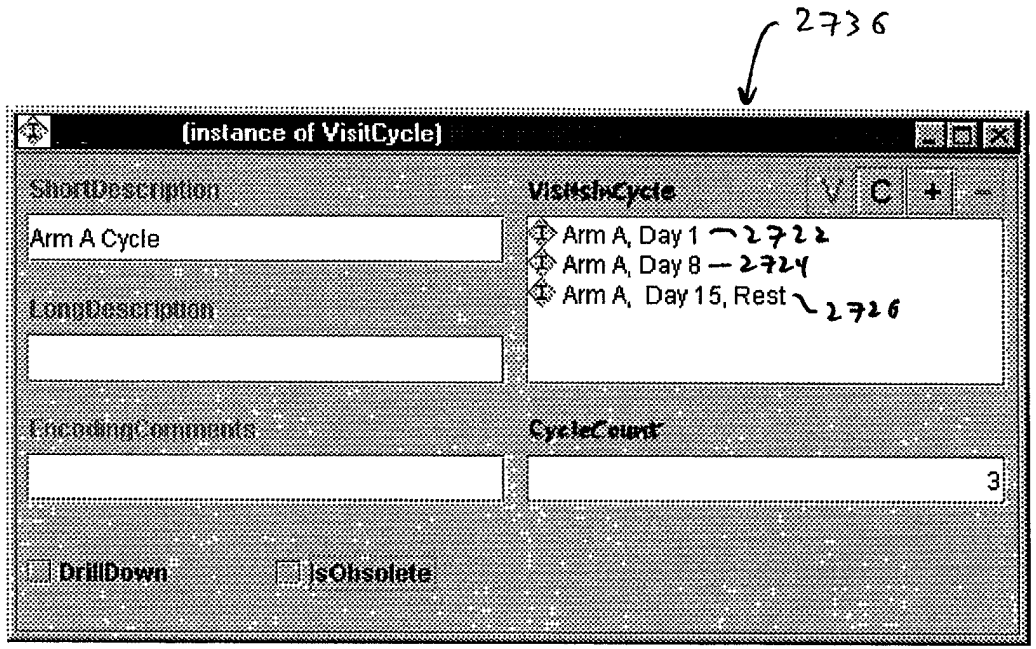


Fig. 33

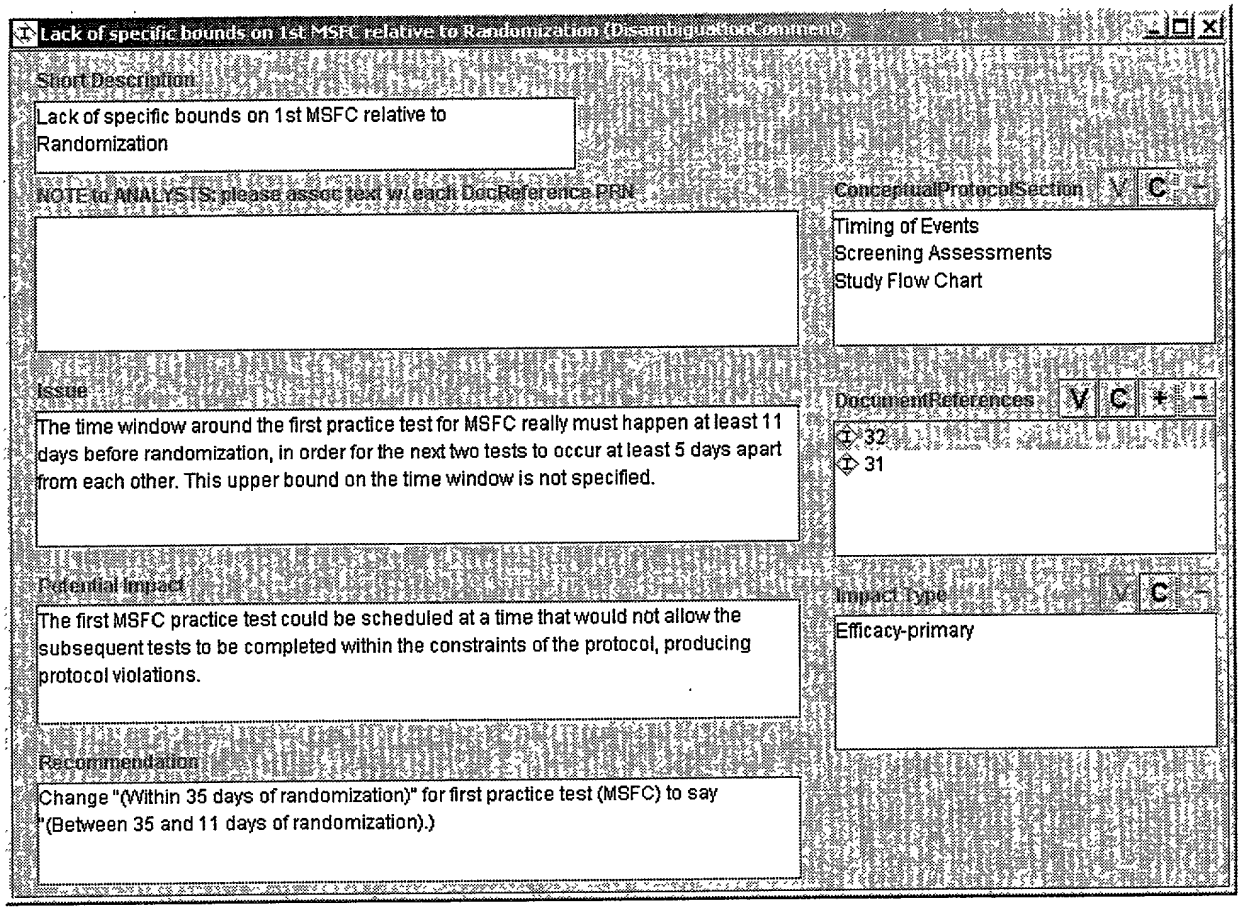

Lack of specific bounds on 1st MSFC relative to Randomization (DisambiguationConcept)
Short Description
Lack of specific bounds on 1st MSFC relative to Randomization
NOTE to ANALYSTS: please assoc text w/ each DocReference PRN
ConceptualProtocolSection
Timing of Events
Screening Assessments
Study Flow Chart
Issue
The time window around the first practice test for MSFC really must happen at least 11 days before randomization, in order for the next two tests to occur at least 5 days apart from each other. This upper bound on the time window is not specified.
DocumentReferences
32
31
Potential Impact
The first MSFC practice test could be scheduled at a time that would not allow the subsequent tests to be completed within the constraints of the protocol, producing protocol violations.
Impact Type
Efficacy-primary
Recommendation
Change "(Within 35 days of randomization)" for first practice test (MSFC) to say "(Between 35 and 11 days of randomization).)

Fig. 34

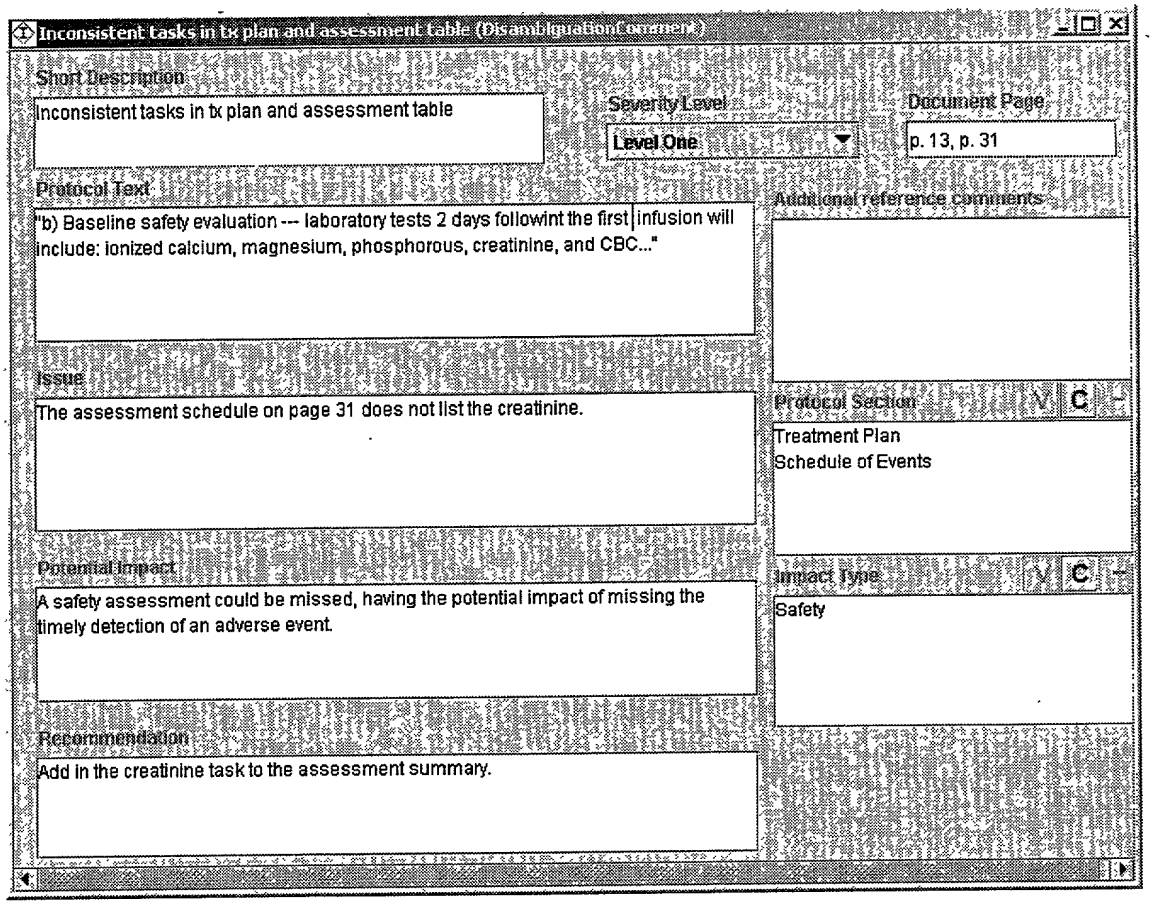
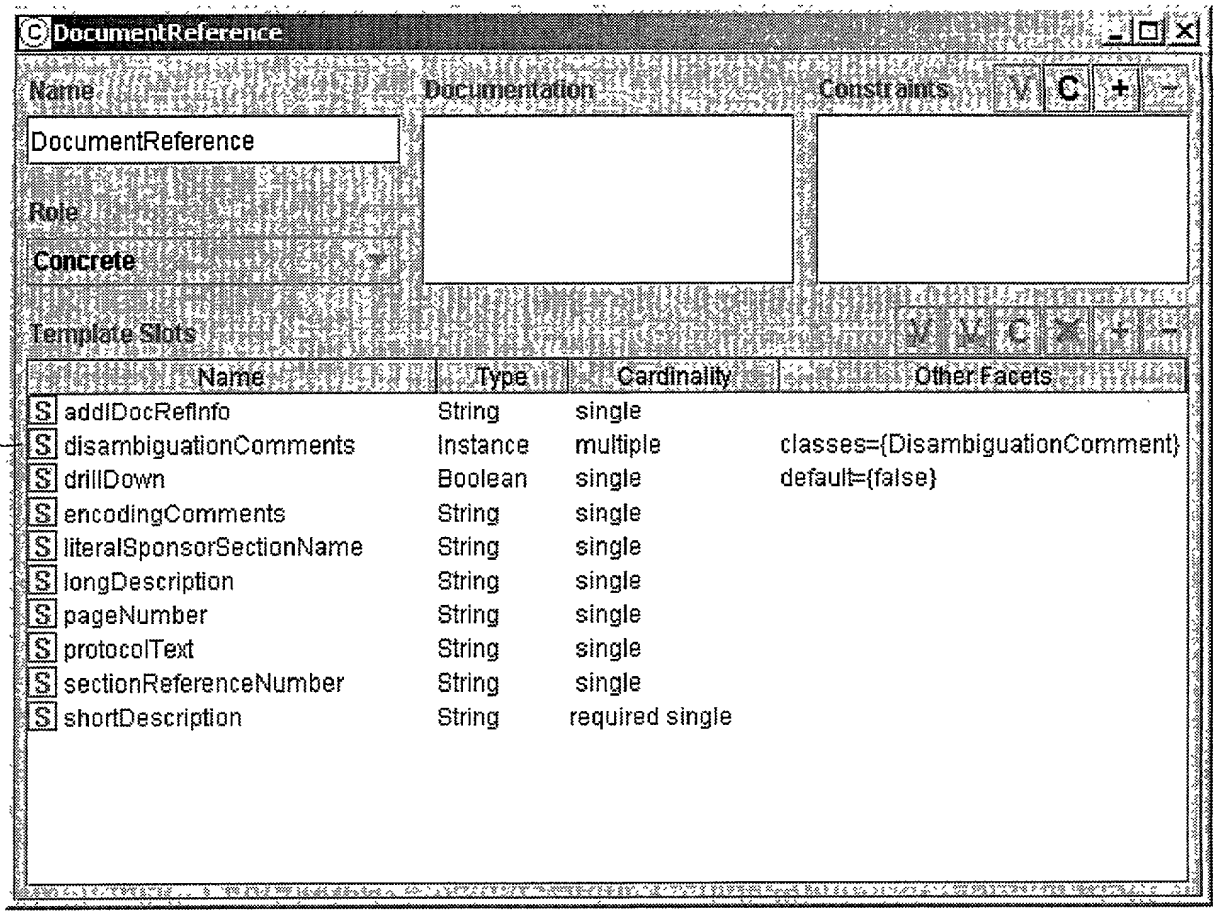

Inconsistent tasks in tx plan and assessment table (Disambiguation comment)
Short Description
Inconsistent tasks in tx plan and assessment table
Severity Level
Level One
Document Page
p. 13, p. 31
Protocol Text
"b) Baseline safety evaluation --- laboratory tests 2 days followint the first infusion will include: ionized calcium, magnesium, phosphorous, creatinine, and CBC..."
Additional reference comments
Issue
The assessment schedule on page 31 does not list the creatinine.
Protocol Section
Treatment Plan
Schedule of Events
Potential Impact
A safety assessment could be missed, having the potential impact of missing the timely detection of an adverse event.
Impact Type
Safety
Recommendation
Add in the creatinine task to the assessment summary.

Fig. 35

920



3610

Fig. 36

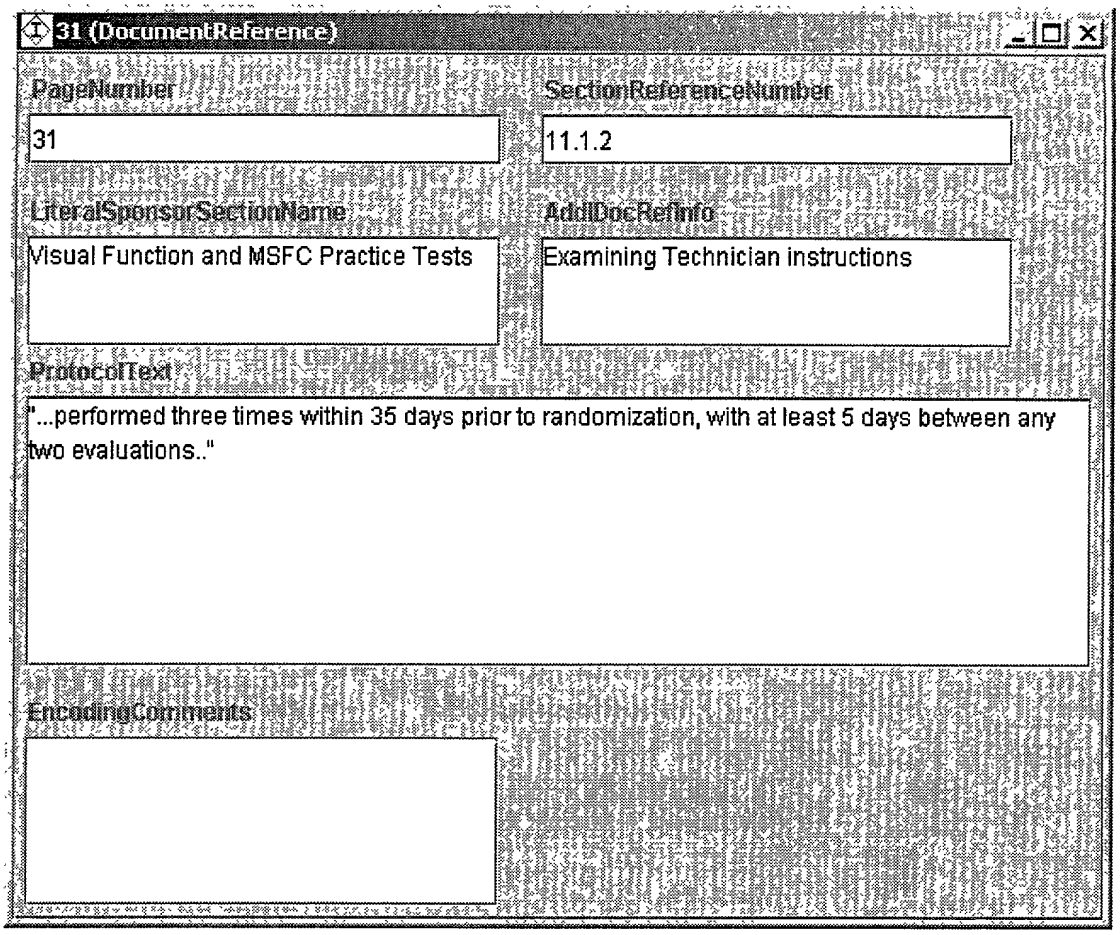

31 (DocumentReference)
PageNumber
31
SectionReferenceNumber
11.1.2
LiteralSponsorSectionName
Visual Function and MSFC Practice Tests
AddlDocRefInfo
Examining Technician instructions
ProtocolText
"...performed three times within 35 days prior to randomization, with at least 5 days between any two evaluations.."
EncodingComments

Fig. 37

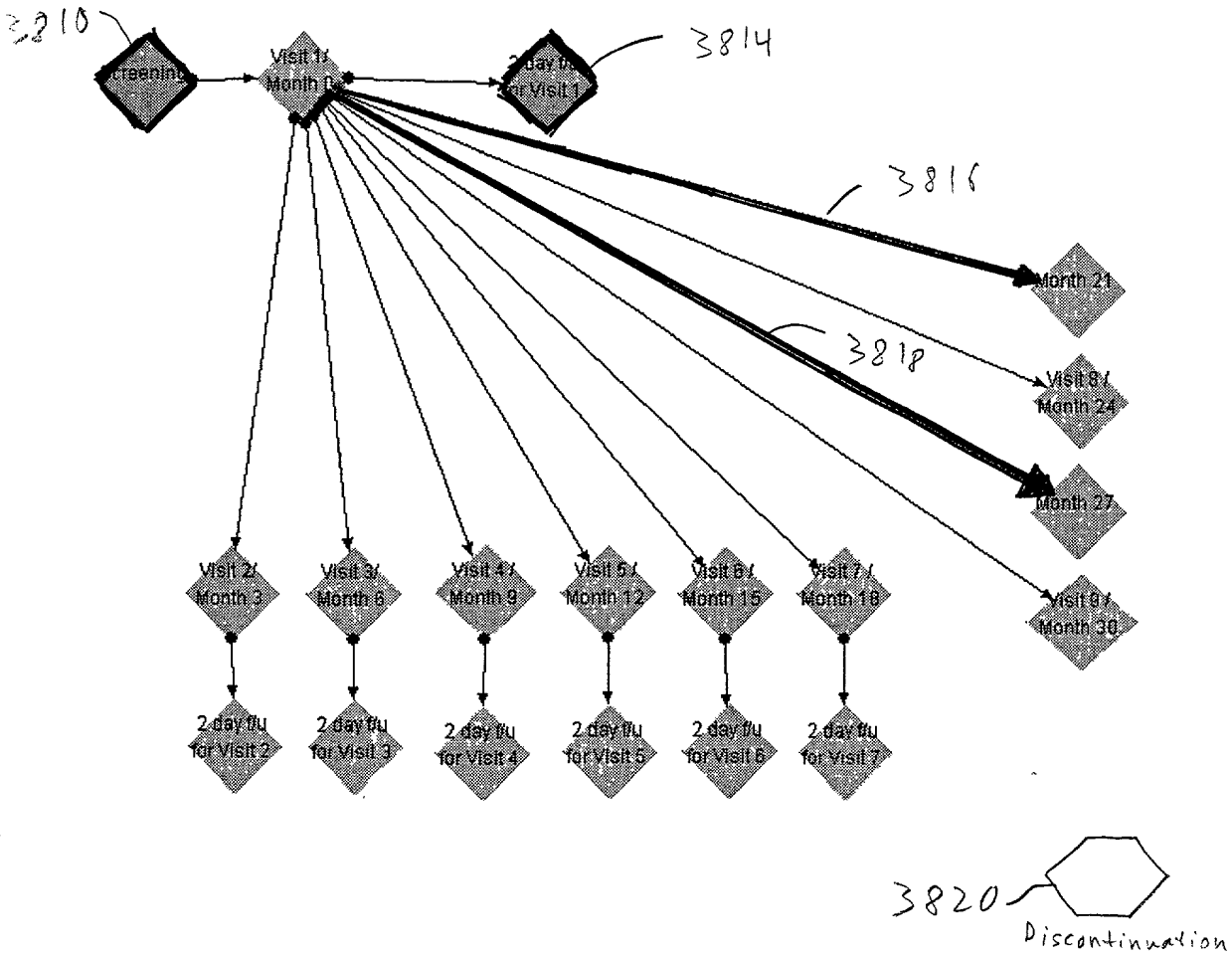

3810
3814
3816
3818
Screening
Visit 1/ Month 0
2 day f/u for Visit 1
Month 21
Visit 8/ Month 24
Month 27
Visit 9/ Month 30
Visit 2/ Month 3
Visit 3/ Month 6
Visit 4/ Month 9
Visit 5/ Month 12
Visit 6/ Month 15
Visit 7/ Month 18
2 day f/u for Visit 2
2 day f/u for Visit 3
2 day f/u for Visit 4
2 day f/u for Visit 5
2 day f/u for Visit 6
2 day f/u for Visit 7
3820
Discontinuation

Fig. 38

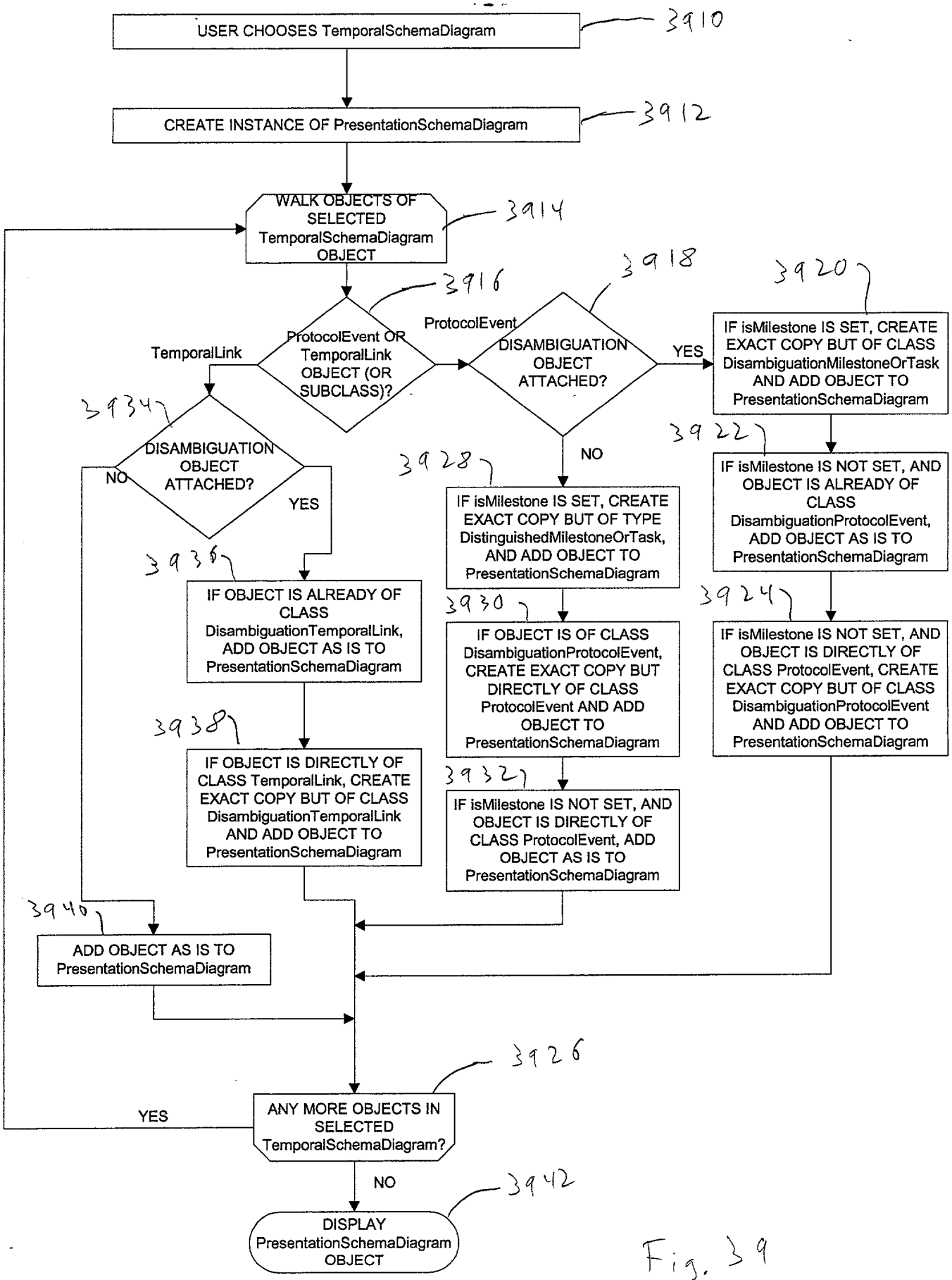

USER CHOOSES TemporalSchemaDiagram
3910
CREATE INSTANCE OF PresentationSchemaDiagram
3912
WALK OBJECTS OF SELECTED TemporalSchemaDiagram OBJECT
3914
ProtocolEvent OR TemporalLink OBJECT (OR SUBCLASS)?
3916
TemporalLink
ProtocolEvent
DISAMBIGUATION OBJECT ATTACHED?
3918
YES
NO
IF isMilestone IS SET, CREATE EXACT COPY BUT OF CLASS DisambiguationMilestoneOrTask AND ADD OBJECT TO PresentationSchemaDiagram
3920
IF isMilestone IS NOT SET, AND OBJECT IS ALREADY OF CLASS DisambiguationProtocolEvent, ADD OBJECT AS IS TO PresentationSchemaDiagram
3922
IF isMilestone IS NOT SET, AND OBJECT IS DIRECTLY OF CLASS ProtocolEvent, CREATE EXACT COPY BUT OF CLASS DisambiguationProtocolEvent AND ADD OBJECT TO PresentationSchemaDiagram
3924
DISAMBIGUATION OBJECT ATTACHED?
3934
NO
YES
IF OBJECT IS ALREADY OF CLASS DisambiguationTemporalLink, ADD OBJECT AS IS TO PresentationSchemaDiagram
3936
IF OBJECT IS DIRECTLY OF CLASS TemporalLink, CREATE EXACT COPY BUT OF CLASS DisambiguationTemporalLink AND ADD OBJECT TO PresentationSchemaDiagram
3938
IF isMilestone IS SET, CREATE EXACT COPY BUT OF TYPE DistinguishedMilestoneOrTask, AND ADD OBJECT TO PresentationSchemaDiagram
3928
IF OBJECT IS OF CLASS DisambiguationProtocolEvent, CREATE EXACT COPY BUT DIRECTLY OF CLASS ProtocolEvent AND ADD OBJECT TO PresentationSchemaDiagram
3930
IF isMilestone IS NOT SET, AND OBJECT IS DIRECTLY OF CLASS ProtocolEvent, ADD OBJECT AS IS TO PresentationSchemaDiagram
3932
ADD OBJECT AS IS TO PresentationSchemaDiagram
3940
ANY MORE OBJECTS IN SELECTED TemporalSchemaDiagram?
3926
YES
NO
DISPLAY PresentationSchemaDiagram OBJECT
3942

Fig. 39

DISAMBIGUATION FINDINGS

Item	Impact Type	Protocol Section	Description	Document Reference
1	Safety Efficacy-primary Efficacy-secondary	Protocol Summary Study Flow Chart	**Issue:** The description in the Protocol Synopsis of when assessments should be performed after 16 weeks is not consistent with Appendix I Schedule of Assessments. **Potential Impact:** Confusion as to when to perform these evaluations (clinical parameters and safety assessments) could result in inconsistent and inaccurate collection of data for the study. **Recommendation:** Revise sentence in the Protocol Synopsis to read, "After 16 weeks these evaluations will be performed every two to "four" months…" in order to be consistent with the timepoints indicated in Appendix I Schedule of Assessments.	*Pg. 12; Section Protocol Synopsis; Procedure; Paragraph 6*: "Clinical parameters (ACR core set) and safety assessments (adverse events and laboratory parameters) will be performed at baseline and then at monthly intervals up to 16 weeks. After 16 weeks these evaluations will be performed every two to three months, up to 104 weeks."

Fig. 40

Item	Impact Type	Protocol Section	Description	Document Reference
4	Safety Accrual	Screening Assessments Study Flow Chart	**Issue:** The protocol text specifies that if an analysis with evidence of seropositivity was performed within 6 months before screening, then rheumatoid factor testing will not have to be performed at screening. However, this is not noted in Appendix I Schedule of Assessments. **Potential Impact:** Unnecessary analysis performed at screening. **Recommendation:** Add a footnote to the Rheumatoid Factor assessment in Appendix I to clarify that documented evidence of seropositivity is acceptable as screening data if obtained within 6 months before screening.	*Pg. 28; Section 8.6.2; Rheumatoid Factor*: "Unless there is documented evidence of rheumatoid factor titre within 6 months before screening a blood sample for this analysis will be taken." *Pg. 41; Section Appendix I; Schedule of Assessments*

Fig. 41